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THE AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

FIRST DAY, JUNE 20, 1946

THREE CASES OF TESTICULAR TUMOR

JOHN A. TAYLOR, M.D.
New York, New York

During the recent war, E. C. Lowry analyzed 100 cases of testicular tumor. It was interesting to note that they reported testicular tumors accounting for 70 per cent of all genito-urinary neoplasms in the Army. J. L. Barner reported sixty-five case, and Friedman and Lewis reported eighty cases. This is easily explained because of the age group, testicular tumors being most prevalent in young adult life. The subject was a most important one in the Medical Corps. In reviewing the reports, one is impressed with the fact that our treatment of testicular tumors is not only unsatisfactory but has changed little over the years. There has not been sufficient time to evaluate the cure in these Army cases. There has been little reduction in the mortality rate, and it is difficult to explain the difference between cure and a fatal result in any given case.

Formerly great emphasis was placed on the hormonal tests; but these have proved of little value except that they are strongly positive in the most malignant form, chorionepithelioma.

Radical dissection of the lymphatics is of questionable value because of the usual bilateral metastatic involvement. Barringer, in a study of autopsy material, reported 72 per cent of bilateral involvement of the abdomen either by glands or metastatic involvement of intra-abdominal organs.

Radiotherapy seems to offer the best prognosis. It should be employed in all cases following surgical removal because paradoxically Barringer reports a much better percentage of five-year cures with adenocarcinoma with metastasis than with seminoma with metastasis, a much more radiosensitive tumor. Pendergrass et al. in the current issue of *Roentgenology* advocated preoperative or immediate postoperative irradiation in all patients with a malignant

tumor of the testis, regardless of the presence or absence of clinical evidence of metastases. It is thought that the best treatment which we have to date is a course of preoperative x-ray, inguinal excision, and postoperative x-ray. It is needless to say that early recognition is very important, and in these days of public health education, we may get these tumors earlier.

CASE REPORTS

Case 1.—B. W. S., a man aged twenty-nine, first seen in October, 1927, was referred by a gynecologist who was investigating his wife because they had never had any children. A condom specimen which he brought in was normal. When an enlarged right testicle was found on examination, he admitted that he had noticed the swelling for four months but had not been concerned about it. Wassermann test was negative. Orchidectomy was advised and done under local anesthesia in St. Luke's Hospital on October 31, 1927.

Pathological report (Dr. Leila C. Knox): "Macro-specimen consists of a testicle which measures 8 by 6 by 5 cm. The epididymis and 4 cm. of vas are included. The portion of the tunica vaginalis covering the testicle is smooth, white and glistening. The entire mass, except for a narrow rim of peripheral testicular tissue, 0.5 cm. in diameter, is made up of a pinkish, greyish, white cellular tumor, apparently with little stroma. The cord and vas deferens show no involvement. Microsections through the testicle and including the tumor show the tubules of the testis are somewhat atrophic, although the epithelial lining appears fairly intact in some of them. There is no evidence of infection. Continuous with this is a tumor which has overgrown and caused the atrophy of the glands and tubules. This is very cellular, the nuclei being large and distinct and the cytoplasm very slightly granular or clear. Mitoses are numerous. The stroma is very scanty. This is the type of tumor which is usually believed to arise from the germinal epithelium of the mature gland, known as either a seminoma or a carcinoma. The vessels of the cord and vas show no tumor formation" (Fig. 1, *A*).

He had postoperative x-ray therapy over a period of three months; the dosage was not recorded.

He was then well until April, 1932, when he returned because of a swelling in his left testicle which he had noticed for about six months. The testicle was enlarged, smooth and hard. There were no clinical or radiographic evidences of metastasis. A-Z test was negative. He was sexually potent.

A left orchidectomy was performed in St. Luke's Hospital under local anesthesia.

Pathological report (Dr. L. C. Knox): "Gross specimen consists of left testicle and epididymis. The testicular tissue appears as a small bar at the hilus and as a shell over the lower pole of an ovoid tumor.

The tumor substance is yellowish, white, soft and friable, and is highly vascularized. The epididymis and vas and contiguous fascial tissues are very edematous and show numerous small thrombosed vessels. No gross invasion by tumor can be made out in this region.

"Microscopic sections of the mass on the surface of the testis show it to be epididymis with considerably cystic dilatations of the tubules. Their lumina are empty and no tumor is seen in this portion of the material. The vas deferens is also relatively normal. There is no infiltration of the cellular tissue, nor of the lymphatics around it.

"Sections of the tumor in the testis show no normal structures, but a very cellular tumor with large spherical nuclei and only a very slight amount of supporting stroma in which there are a few delicate blood vessels. The stroma is generally infiltrated with lymphocytes. The nuclei are of the type which are probably derived from the germinal epithelium. The tumor shows no teratoid structure. All of the tumor cells are of the same variety. This tumor is also identical with the one previously removed. Flattened over the surface of this tumor, there are a few atropic tubules of the testis and a few groups of interstitial cells. These are being invaded by the growth." Diagnosis: seminoma (Fig. 1, *B*).

Postoperative x-ray treatment over the usual portals, front and back, were given. By x-ray the chest was clear on May 2, 1933. The patient had no symptoms. In 1938, he still had no complaints; x-ray examination was negative. He was still sexually potent with oretone. He was one of the first patients who had taken testosterone as replacement therapy. Before he took testosterone, he was functioning monthly. By means of testosterone intramuscularly, he was able to function weekly. The texture of his skin improved and the hair on his skin returned to a masculine distribution and texture.

During World War II, he was a correspondent and traveled all over the world. He returned to this country in June, 1945, and came to the hospital for a complete check-up. His examination, including an x-ray of chest, was negative. He is now a Washington correspondent and reported by telephone that he is feeling well and working hard in his new position.

Comment: This is an interesting case of bilateral testicular tumor with a cure extending over nineteen years from the first orchidectomy and fourteen years from the second.

Case 2.—T. S., a man aged twenty-six years, was admitted to the Hospital for the Ruptured and Crippled on May 17, 1932. He complained of a swollen left testicle for eight months. Physical examination showed a normal boy with a left testicle which was swollen twice the normal size, and was firm and slightly irregular. There were no palpable nodes in either the inguinal or lumbar regions. X-ray of chest was negative. A-Z test was negative.

The testicle was removed through an inguinal incision, the cord being first ligated and ablated at the level of the internal ring and the testicle removed last.

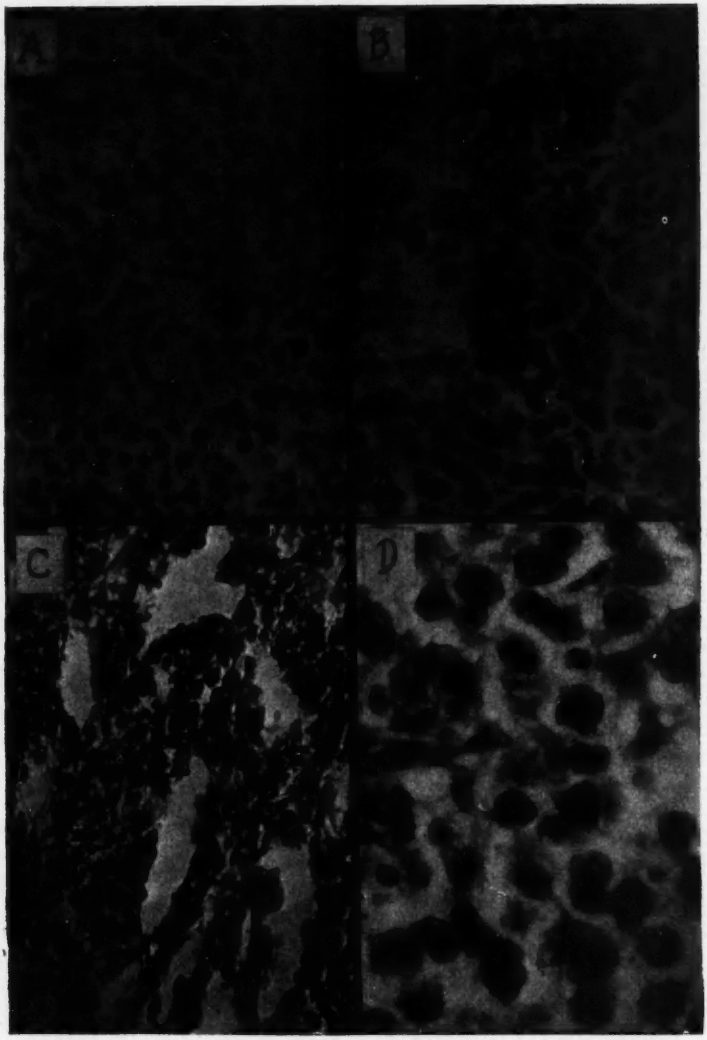

Fig. 1. (*A*) Case 1. Seminoma involving left testis removed October, 1927. Tumor cells of uniform size, cytoplasm clear, nuclei spherical. × 875. (B) Seminoma removed May, 1932. Type same as previous tumor. Note groups of lymphocytes alternating with tumor cells. × 875. (C) Case 2. Tumor of testis. Teratoma composed of sheets of undifferentiated epithelium with poorly defined glandular spaces. × 200. (D) Seminoma of testis removed in December, 1944. Tumor consists of masses of spherical cells, often with clear cytoplasm and dense nucleoli. × 875.

The pathological report showed a testicle measuring 7 by 6 cm. which on section showed the normal tissue replaced by a soft friable mass.

Microscopic examination showed a diffusely infiltrating mass of undifferentiated epithelial cells arranged in compact masses and showing many mitotic figures. Diagnosis: teratoma (Fig. 1, *C*).

He had a course of postoperative x-ray therapy but did not tolerate it very well.

In October, 1932, five months after operation, a mass, which was undoubtedly a metastatic lesion, appeared in the left side of the abdomen. This disappeared with radiotherapy.

On July 11, 1933, x-ray examination showed that the lung fields were clear. He was well until May, 1942, when a pre-induction x-ray revealed a tuberculous lesion in the right apex and he was deferred from military service. The diagnosis was confirmed at St. Luke's Clinic and he was hospitalized at Lenox Hill Hospital for three months and subsequently at Otisville for five months, when he was discharged as arrested.

A tonsillectomy was performed at St. Luke's Hospital on May 23, 1943, for recurrent tonsillitis. At this time his right testicle was normal.

In December, 1944, he returned to the clinic because of an enlarged right testicle which was nodular, hard and painless. Tuberculosis of the epididymis and testicle was considered. An x-ray of the chest revealed "fibrocalcific infiltration in right apex; no activity . . . ." "Friedman's modification of the A-Z test showed negative animal reactions for the hormones, prolan A and prolan B."

Under local anesthesia a resection of the cord and testicle was done, beginning at the level of the internal ring. At the request of the patient two vitallium balls were placed in the scrotum.

Pathological report (Dr. L. C. Knox): "Gross specimen of a right testicle which is 6 by 5 by 4.5 cm. and has been laid open. The surface is lobulated and on section there are soft necrotic areas scattered through rather firm growth which has replaced the normal structure of the gland. There are also some bright yellow areas, the largest 12 mm. long. Seven centimeters of the cord and epididymis are attached. The structure of the cord appears normal and the epididymis does not appear to be involved in the growth.

"Microscopic section show that the normal structures are replaced by a large mass of tumor. This growth is obviously malignant, consists of many spherical epithelial cells loosely attached to each other and to the connective tissue around the blood vessels. Their nuclei are hyperchromatic, some of them vesicular. They show very little differentiation and mitoses are not prominent. This tumor has the appearance of one arising in the germinal epithelium. The groups of tumor cells are found within the veins, these being apparently tumor emboli. Diagnosis: seminoma (Fig. 1, *D*).

He had postoperative x-ray therapy through the usual portals.

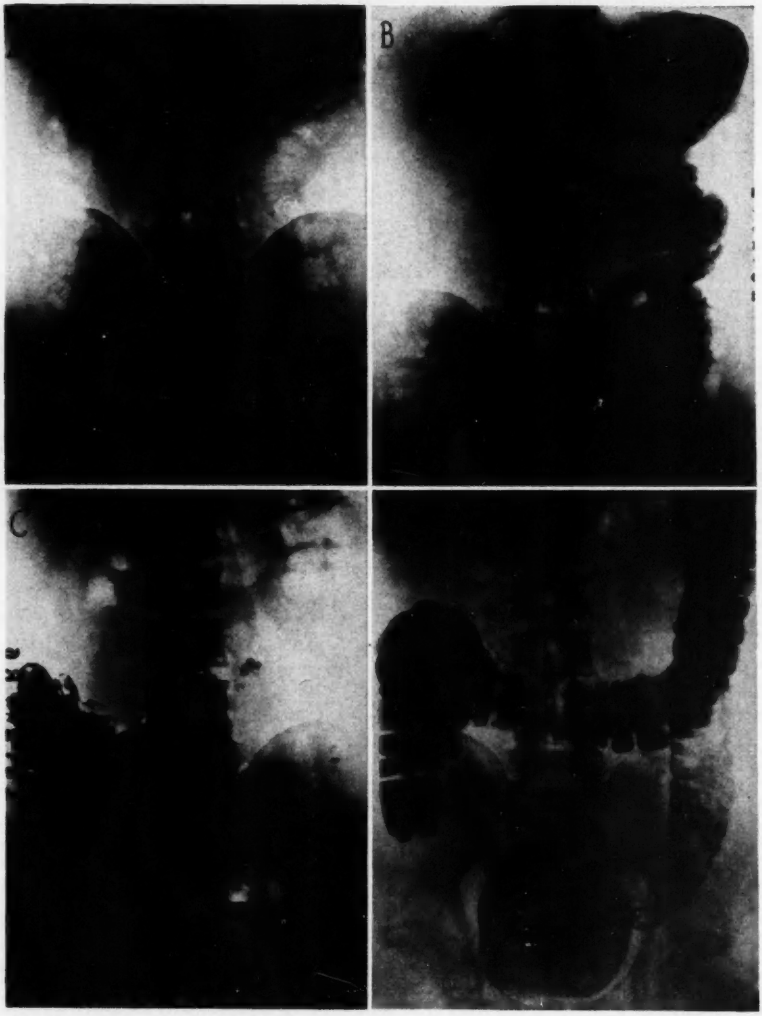

Fig. 2. Case 2. (*A*) Excretory urogram shows slight lateral displacement of upper right ureter and slight delay in emptying. (*B*) X-ray shows medial displacement of descending portion of duodenum by metastic tumor. (*C*) Mass is also producing downward displacement of hepatic flexure as demonstrated in six-hour examination. (*D*) X-ray (Clysma) taken June 12, 1936, after radio therapy, shows absence of pressure on colon.

On March 4, 1946, he returned because of a mass in the right side of the abdomen. Excretory urograms showed prompt excretion on both sides with good concentration. There was a round, soft tissue mass of homogenous density, measuring approximately 2½ inches in diameter to the right of the third and fourth lumbar vertebrae. This mass was producing slight lateral displacement of the upper right ureter and slight delay in emptying on this side. No bone metastases were seen. (Fig. 2, *A*).

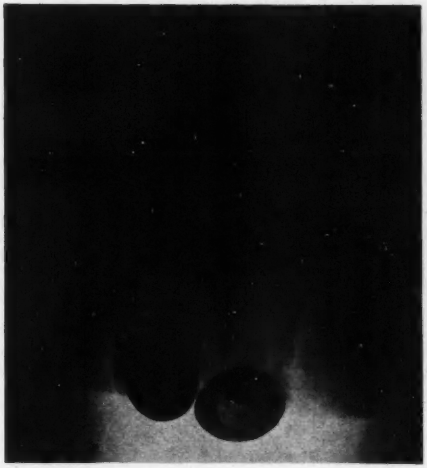

Fig. 3. Case 2. X-ray of scrotum showing vitallium balls in place.

The gastrointestinal series (April 4, 1946) showed . . . "the descending portion of the duodenum is displaced medially by a round soft tissue tumor located just below the kidney (Fig. 2, *B*). The mass is also producing downward displacement of the hepatic flexure as demonstrated in the six-hour examination (Fig. 2, *C*)."

Because he tolerated x-ray therapy poorly, he received fifteen treatments of 100 r each in a month, and the mass disappeared. An x-ray (Clysma) on June 12, 1946, showed no growth and the ascending and transverse colon in a normal position without pressure. (Fig. 2, *D*).

An x-ray of the scrotum showed the vitallium balls in place (Fig. 3).

Comment: This case is interesting: (1) as a case of bilateral tumor with metastases and a cure, extending back to the first orchidectomy of fourteen years; (2) because of the presence of a teratoma on the left side and a seminoma on the right; (this is not so remarkable if one accepts the teaching of Ewing that these testicular tumors all arise

from a totipotent cell and that their differences in structure depend on the rate of growth of cells of different types); (3) the co-existence of pulmonary tuberculosis. It has often been reported that when these testicular tumors begin to metastasize, they are often confused with tuberculosis because of the loss of weight and the chest lesion. It was thought at first in this case that the boy was beginning to get pulmonary metastases. A study of the chest films (Fig. 4, *A*) showed without

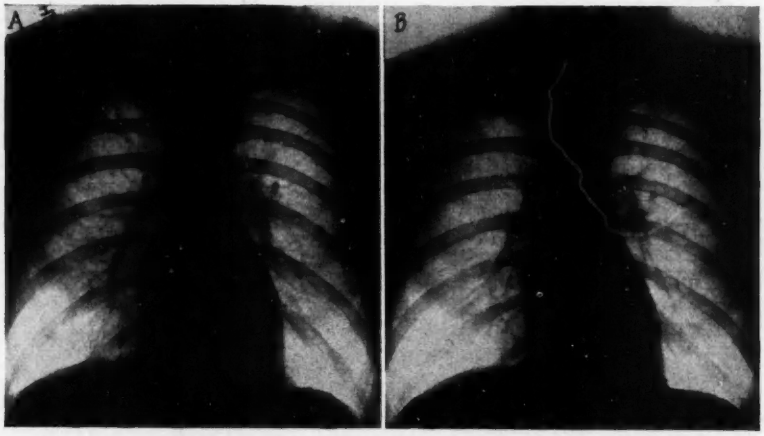

Fig. 4. Case 2. (*A*) X-ray of chest (1942) shows soft, diffuse infiltration of tuberculosis. (*B*) X-ray of chest (1944) shows fibrocalcific replacement of tuberculous lesion.

a doubt, the soft diffuse infiltration of the apex, typical of tuberculosis, replaced in a later film (Fig. 4, *B*) with calcification. (4) Replacement of testicles with vitallium balls produced the desired result very satisfactorily without any local reaction.

Case 3.—P. R. W., a man, twenty-three years old, first presented himself for examination in August, 1937. He complained of a swelling of his right testicle, first noticed two months earlier. It had remained approximately the same size. He had been kicked in the testicle while in swimming one month before he noticed the swelling.

General examination was essentially negative except for a bad recent acne and a slightly enlarged right breast, which was tender. Examination of scrotal contents showed the left testicle to be normal. The right testicle was about three times normal size, smooth, firm and not tender. There was no clinical evidence of metastasis. An x-ray of the chest was clear. Friedman's modification of the A-Z test was positive. He had two preoperative x-ray treatments, and a right orchidectomy was

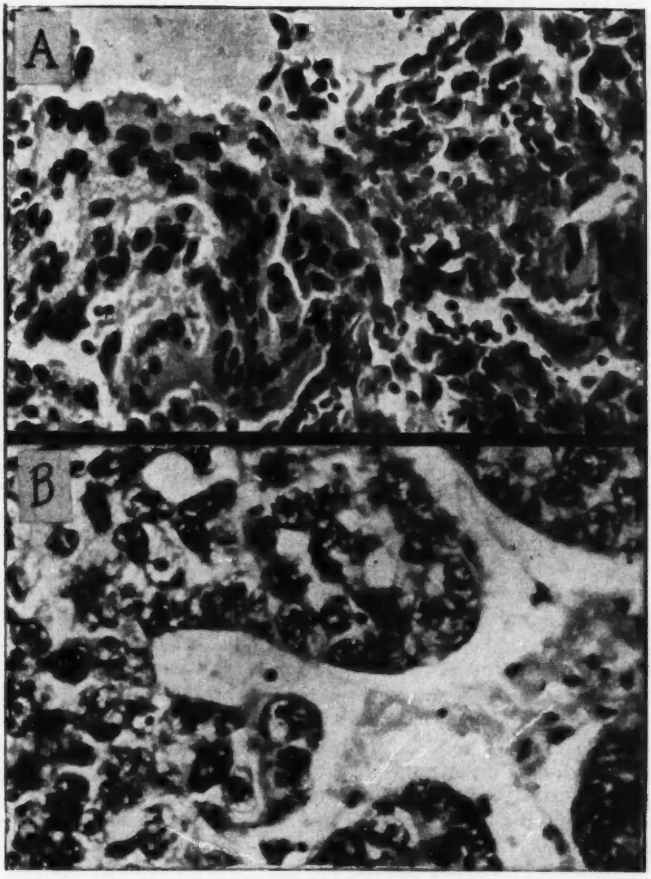

Fig. 5. Case 3. (*A*) Teratoma removed August, 1937. Syncytial cells and large polyhedral cells of Langhans type. This resembles a chorionepithelioma. × 375. (*B*) Another portion of tumor shows sheets of small, undifferentiated epithelial cells bordering large blood sinuses. × 375.

performed in St. Luke's Hospital on August 25, 1937. The resection of the cord and testicle was begun at the level of the internal ring and carried caudad, the testicle being delivered through the inguinal incision.

The pathological report by Dr. Leila C. Knox was as follows: "Gross specimen consists of right testis. It measures 12 by 6 by 6 cm. and is rather soft in consistency. On cut section, the capsule is found to be under considerable tension. Inside there is a rim 0.5 to 1 cm. in thickness of normal testicular tissue. Inside this is an encapsulated tumor which shows large and small cystic spaces filled with blood and soft yellowish friable tissue. Much of the tissue between the cystic area is edematous and gelatinous in consistency, and greenish brown in color. The tumor does not seem to have grown through the capsule at any point.

"Microscopic sections of this tissue show some of the testicular tubules, in all of which there is an inflammatory and degenerative process but with preservation of many of the epithelial tubules. Continuous with this and invading it, is an extensive neoplasm, teratoid in type, with malignant connective tissue and epithelial areas as well as ducts, and glands and tubules, which do not in themselves appear malignant, but are a more highly differentiated part of the tumor. There is a large amount of the stroma which is extremely edematous and contains small, plump, connecting tissue nuclei. The most cellular and probably most malignant fraction of the tumor is a chorionepithelioma consisting of sheets of undifferentiated epithelial cells as well as many syncytial cells which surround lakes of blood, contain many hyperchromatic nuclei and show other detailed morphology which is found in these tumors. This is probably a high malignant growth and may be expected to metastasize to the lungs especially."

Diagnosis: teratoma of right testis with chorionepithelioma (Fig. 5).

Postoperatively, he had 3500 r through the usual portals and four mediastinal treatments because of the reported malignancy of the tumor.

It was interesting to note a very startling postoperative improvement in the acne. The gynecomastia disappeared.

He was followed very carefully until March, 1942, and there was never any clinical, roentgenologic or hormonal evidence of recurrence. He had gained 15 pounds at that time.

Both he and his fiancee decided to get married in spite of his history of malignancy. They moved south where he has been active with one of the air lines. They have two children, two years and two months old. His mother, returning from a visit with him on June 6, 1946, reported that he is enjoying excellent health and working hard.

Comment: This case is interesting because (1) it is a nine-year cure of a chorionepithelioma; (2) the excessive hormonal secretion was evidenced not only in the urine but with a gynecomastia and acne, both of which disappeared after the orchidectomy; (3) preoperative x-ray of a testicle has been discouraged by some because it is supposed to

destroy the germinal layer of the other testicle. This man has had two children.

CONCLUSIONS

A case of bilateral seminoma with a cure extending over nineteen years from the first orchidectomy and fourteen years from the second, has been described.

A case of bilateral testicular tumor has been described—a teratoma on the left and a seminoma on the right, both with metastasis —extending over fourteen years from the first orchidectomy.

A case of chorionepithelioma with a nine-year cure has been described.

The writer is indebted to Dr. Francis Carter Wood for the excellent micro-photographs and legends.

2 E. 54th St., New York 22, N. Y.

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PATENT URACHUS ASSOCIATED WITH URINARY TUBERCULOSIS

JAMES C. McCLELLAND, M.D., and KENNETH F. DAVIS, M.D.

From the Urological Service of the Toronto Hospital for Consumptives, Weston, Ontario, Canada

Various lesions of the urachus have been encountered, such as cysts, new growths, inflammations, congenital persistence of the tract, and urachal calculi. Cullen in his book *The Umbilicus and its Diseases* (1916) has quoted two cases of tuberculosis of the urachus, one reported by Briddon and Eliot, and another reported by J. R. Eastman. The following case report is of a patient with advanced tuberculosis in the urinary tract.

A swelling developed at the umbilicus which was suspected of being an abscess at first, but later was found to be a tract leading from the umbilicus to the bladder. A catheter was passed from the umbilicus along the tract to the bladder and the urine drained from the catheter for months until the patient died from advanced renal tuberculosis in her remaining kidney, and uremia.

CASE REPORT

D. G., a girl aged fourteen and one-half years, was admitted September 22, 1942, to Weston Sanatorium, and died June 3, 1945, aged seventeen, after 985 days in the hospital.

She gave a history of having been in the Sanatorium in Ottawa from the age of three to the age of eleven (eight years) under treatment for tuberculosis of the right ankle. She was in bed three years, then on crutches and finally was walking with the ankle healed and ankylosed.

For two years (from eleven to thirteen years of age) she lived in a convent and was admitted to the Ottawa General Hospital where the right kidney was removed for tuberculosis. She was discharged in three months, but returned nine months later (January, 1942) in a moribund condition. At this time it was stated that a pelvic abscess developed, and that it ruptured through the umbilicus and continued to drain until her admission to the Weston Sanatorium, September 22, 1942. Her general health improved and she gained 20 pounds in weight, although there was a purulent discharge from the umbilicus. Tubercle bacilli were neither suspected nor recognized.

The umbilicus sinus healed two months after admission, and she gained slightly in weight.

One year after admission (September, 1943) a left perinephric abscess was drained. Cultures showed B. coli, but those for tubercle bacilli were negative. Healing of the abscess was not complete for nine months.

In May, 1944, twenty months after admission, extreme lassitude and intense pigmentation of the skin suggested Addison's disease, and the patient did well on sodium chloride, 75 gr. per day. Her weight increased, and occupational therapy was commenced again.

In June, 1944, twenty-one months after admission, suprapubic dis-

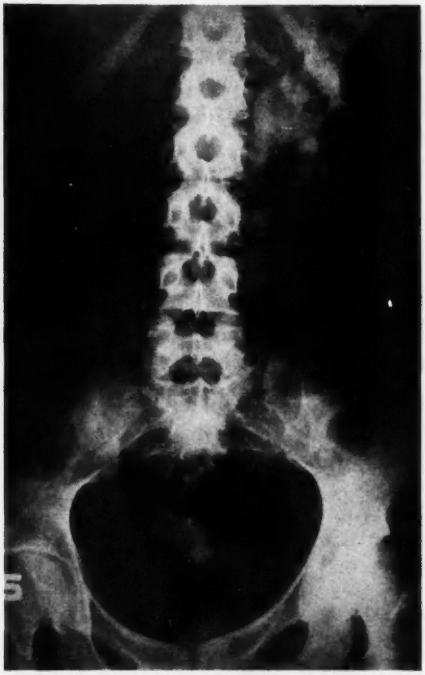

Fig. 1. Forty-five minute intravenous urogram which shows dilatation of major and minor calyces, suggesting cavitation of tuberculosis.

comfort, redness and swelling of the umbilicus appeared; the red area was incised, and 20 c.c. liquid pus were recovered, a culture of which yielded B. coli. A copious liquid discharge, which was recognized as urine, came away. A catheter was passed through the opening in the umbilicus into the bladder, through which urine drained until the patient died from uremia ten and one-half months later.

There was a gradual decrease in the amount of urine passed, but the nonprotein nitrogen increased to 96 mg. The abscess in the left flank appeared again and was incised. It continued to drain until her death, but a culture of the pus did not yield tubercle bacilli.

Cystoscopy showed that the bladder capacity was small. There was marked inflammation of the mucosa. The left ureteral orifice was seen, but could not be catheterized. Urine from the bladder showed tubercle bacilli, both on direct smear and culture for tubercle bacilli.

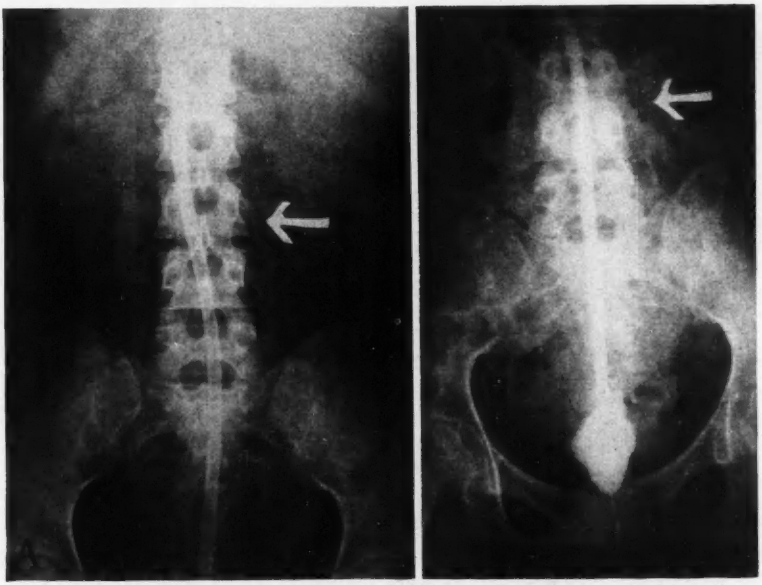

Fig. 2. (*A*) Catheter passed through umbilicus and urachus into bladder. Arrow placed at level of umbilicus. (B) Cystogram taken with catheter through umbilicus. Arrow is at level of umbilicus.

An intravenous pyelogram on March 18, 1943, demonstrated slow excretion from the left kidney, cavitation and dilatation of the pelvis and ureter: a tuberculous kidney (Fig. 1). A cystogram taken September 11 is shown in Figure 2.

Autopsy No. A-14-45 (Dr. E. Massig, Pathologist, Toronto Hospital for the Treatment of Tuberculosis, Weston, Ontario): Renal tuberculosis; patent urachus and sequellae.

"Autopsy confirmed the diagnosis of a patent urachus and tuberculosis of the entire urinary tract. A solitary obsolescent tuberculous lesion was present in the right upper lobe. There was massive amyloi-

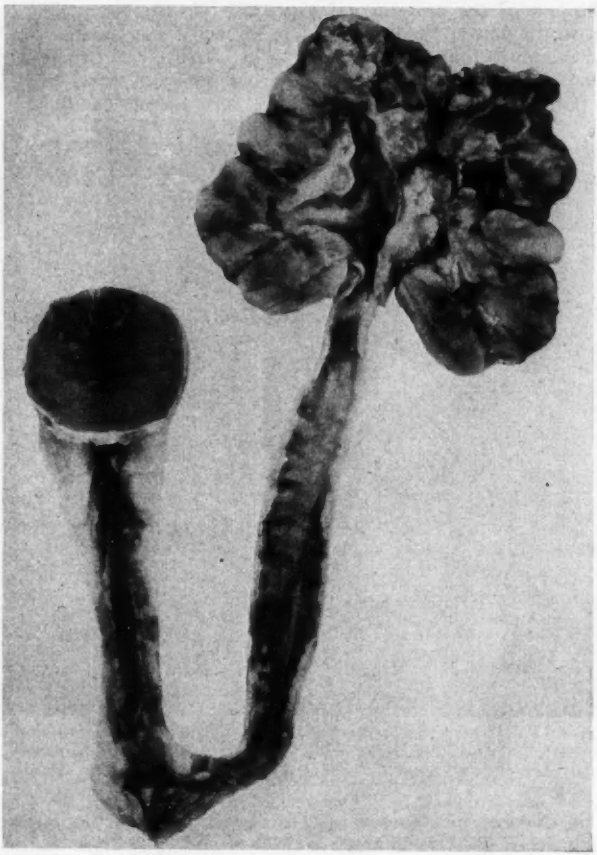

Fig. 3. Autopsy specimen of umbilicus, patent urachus, bladder, left ureter, and left kidney. Note small contracted bladder, dilated urachus, dilated ureter, and cavitation in kidney. Right kidney and ureter were removed at an early operation, and were tuberculous.

dosis of liver, spleen, kidney, adrenal glands and heart and an unusual finding of arteriosclerosis and calcification of the coronary arteries of the heart was seen."

"The urinary bladder was embedded in considerable dense fibrous tissue and was greatly shrunken, so that it appeared to be an irregular saccular continuation of the left ureter. The normal contour was distorted beyond recognition and the trigone and ureteral orifices were obliterated by a markedly thickened, lumpy, edematous, congested, and, in part, hemorrhagic and ulcerated mucosa. This small, contracted bladder presented a congenital anomalous formation, in that at its vertex it opened into a broad channel which again appeared to be merely a continuation of the urinary tract which lay in the midline on the inner surface of the anterior abdominal wall directed upwards toward the umbilicus at which point a cutaneous funnel-shaped opening was seen. This portion represented a patent urachus of approximately the size of an index finger, the lumen of which measured up to 1.5 cm. in diameter, but in its first portion was considerably narrowed and thick walled, sclerotic and fibrous to feel and apparently lined by a mucous membrane which also appeared greatly edematous, congested, hemorrhagic and in part ulcerated. The opening at the umbilicus was depressed and the usual prominence of the stump of the umbilical cord could not be recognized, while the surrounding skin appeared rather deeply pigmented" (Fig. 3).

Microscopic examination: "In the urachus the histological picture was indistinguishable from that of the urinary bladder, and the inflammatory reaction was of the same character, obscuring what may be an ulcerative tuberculous process."

We wish to thank Professor Boyd of the Department of Pathology of the University of Toronto, for his kindness in supplying the photograph of the pathological specimen.

VENOUS INVASION DUE TO URETHROGRAMS MADE WITH LIPIODOL

E. GRANVILLE CRABTREE, M.D.

Boston, Massachusetts

Graphic demonstration by x-ray of invasion of the venous channels from urethrography appears not to have been reported in the American literature, although noted in foreign publications. Adequate reference to the special characteristics of the genito-urinary tract which underlie such an occurrence has been made through reports which led to the assumption that catheter chills are septicemias: Keyes demonstrated that collargol used as a medium for pyelography was seen in the opposite kidney; then there have been few case reports of either venous or lymphatic demonstrations in pyelography as a result of overdistention of the pelvis of the kidney. Sudden deaths from cocaine and other anesthetics when used in the urethra frequently have been reported.

Within the past decade much more extensive use of labile fluids and oil media for injection of the lumina of the genito-urinary organs has been made than previously. Such injections are now commonly made of the uterus and tubes, bladder, urethra, ureters and pelves. From all these procedures instances of invasion of venous channels have been collected in the course of preparation of this paper. Venous invasion from utero-tubograms appears to be most common; that from overdistention of the renal pelvis second in frequency; that from ureterogram least common. Injection of other organs (such as bowel, spinal channels and bile ducts) appears not to produce the clinical signs of systemic invasion in the form of chills and fever comparable to "catheter chills," or x-ray demonstrations of the invasion of vascular channels.

Two considerations appear to weigh heavily in determining the readiness with which channels can be entered from the lumina of genito-urinary organs. One is the great vascularity of all these organs, separated from the lumina by a very thin mucosa; the other, at least in the cadaver, is a remarkable intercommunication of venous plexuses that may be injected from very small veins of the external genitalia or from the corpora.

According to Grauhan, the mucosa of the urethra is 1 mm. in thickness. In the pendulous and bulbous portions of the male urethra this thin membrane overlies loose submucosal tissue which is separated from the thin walled venous channels of the corpus spongiosum by structures which offer little resistance to strain of injection and are easily weakened by infection and instrumentation.

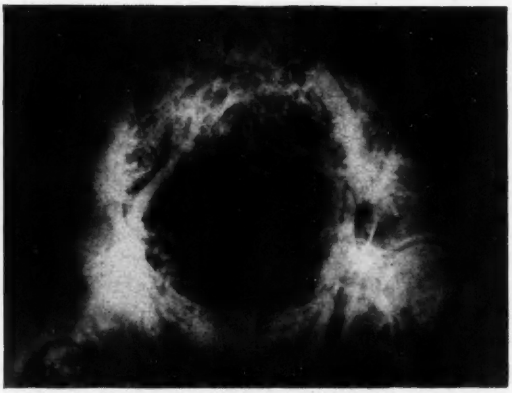

Fig. 1. X-ray of pelvis of cadaver after injection of penile vein with sodium iodide solution to demonstrate venous communications. Picture printed to bring out superficial veins. (Injection by Dr. Henry A. Kontoff.)

They are rich in small vessels, which have wide anastomoses with each other, and which connect with the corpora by small channels and interconnect with the deep vessels of the perineum and the more superficial vessels of the penis and scrotum.

The urethral mucosa is of frail construction. When distended it is only two or three thin, flat cells thick. Stratified squamous, columnar or cuboidal epithelium is found in most of the other hollow viscera. In these the epithelium is practically unalterable on stretching. Where there is great vascularity in the spaces beneath the mucosa of the genito-urintary tract, there are also similar conditions associated with the mucosa of the intestine. Presumably it is the character of the epithelium at fault in the genito-urinary tract.

In the posterior urethra and the prostatic portion there is abundant blood supply of both the mucosa and neighboring structures, but the spongiosum is absent and the surrounding tissues are more

substantial. Yet even here the urethral mucosa, when undergoing distention, is a fragile membrane of few cell layers placed on a bed of almost nonsupporting tissues. Furthermore, the mucosa and its underlying tissues are not constructed to endure stretching as is the bladder, which is known to be resistant to invasion by drugs.

The extent to which widely disseminated injections of the ves-

Fig. 2. X-ray printed to bring out deep vessels of pelvis. (Injection by Dr. Henry A. Kontoff.)

sels of the pelvis, external genitalia, spermatic and ovarian veins, and veins overlying the hip joints and lower spinal region result from injection of superficial vessels of the external genitalia is impressive. Such injections are made with the stream, towards the vena cava. Injections of the dorsal vein of the penis with sodium iodide produce the pictures shown in Figures 1 and 2. Figure 1 has been printed to demonstrate the more superficial vessels, and

Figure 2, the deep vessels. Injection of the corpora has been shown in both cadavers and humans to fill the dorsal vein of the penis through intercommunicating vessels. Similar injections have been made with Latex and with oily media in place of a labile fluid like sodium iodide.

From a survey of the reported vases of venous invasion by media used in urethrography, it is apparent that such permeation of veins can occur either from the use of force from without in making the injection or from force supplied by the bladder and abdominal muscles in voiding against urethral obstruction. Edling believed that the latter form of venous invasion supersedes the former in causing evidences of damage in the form of "catheter chills." He found few instances of reaction to venous invasion produced by external pressure through urethral injection. Factors other than the method of supplying the pressure and the degree of pressure employed must be considered, especially the duration of the period of pressure and consequently the probable amount of infected medium or infected urine which is forced into the circulation.

Of the twenty-seven cases of venous invasion from urethrography reported in the literature, in two instances acute urethral infection alone was adequate for rendering the urethra permeable. There were six urethral strictures, two urethral stones, one injury to the penis, one phimosis and stenosis of the meatus with wedged-in calculus, one stenosis of the prostatic urethra, all previously subjected to instrumentation a few days to one week before injection; the others followed instrumentation, with the exception of four, where no urethral disease or instrumentation was noted or done. It is not easy to find descriptions of technique or the degree of pressure used from the literature.

The material used was uroselectan, iodipin (an oily substance under a German trade name), lipiodol, liquid petrolatum and thorium.

There were four deaths from emboli from oily media and thorium in the twenty-seven cases of venous invasion in the literature. Two resulted from forced dilation of urethral strictures by use of liquid petrolatum; 20 c.c. was used for the procedure. Both patients had hemiplegia within a few minutes. Oil embolism was demonstrated in one; there was an incomplete autopsy in the other. One death from iodipin followed soon after injection. Fat emboli were

demonstrated. One catheter chill resulted after lipiodol and one catheter chill after thorium, with thorium emboli produced throughout both lungs which persisted until death six years later. Thorium was used once after extravasation of urine and gangrene. At death two weeks later, the pyelographic medium was present in all parts of the pelvis, lungs and kidneys. There were no deaths from lipiodol. In one case iodipin disappeared in six weeks from small infarcts in the lung. It disappeared from a larger infarct in the other lung in three months.

There appears not to be a close relation between the amount of medium injected, discomfort produced during injection, or bleeding caused by the injection and the occurrence of venous invasion. In most of the cases in which the phenomenon occurred there was no discomfort and x-ray alone demonstrated the dye in the veins. Injections of 20 c.c. appear to be the most common. Franck quotes Fibiger, who estimated that 50 c.c. oil injected intravenously will cause death from fat embolism, and also Ribert, who considered that 15 to 20 c.c. are adequate for death. Patterson offered a more logical explanation when he suggested that bad results were most likely due to distribution of the oil to vital centers. This may well apply to oil, but thorium produces a permanent lodgement and appears to be an irritant, especially in the lungs. Deaths have been reported from the use of 7 c.c. of 1 per cent cocaine (Czerny), 10 c.c. of alypin (Schonfield and Müller); 10 per cent collargol and 5 c.c. of 3 per cent butylene gave syncope and collapse with recovery (Marcelle and Brochard).

Obviously, a soluble medium avoiding oils, yet viscid enough to be retained in the urethra sufficiently long for exposure to x-ray, would be most desirable for use in urethrography. Labile solutions are unsatisfactory for delineation of pathological changes, and invade the veins, yet are most nearly harmless. One should avoid urethrography in the presence of acute urethritis, and injuries, undue force at injection, and the use of thorium following instrumentation.

The only statistical evidence as to frequency of venous invasion in urethrography is given by Edling, who found that it occured fifteen times in 570 cystourethrographies.

Since there is a tendency for the veins, when invaded, to fill patchily and not completely enough to outline their course, a re-

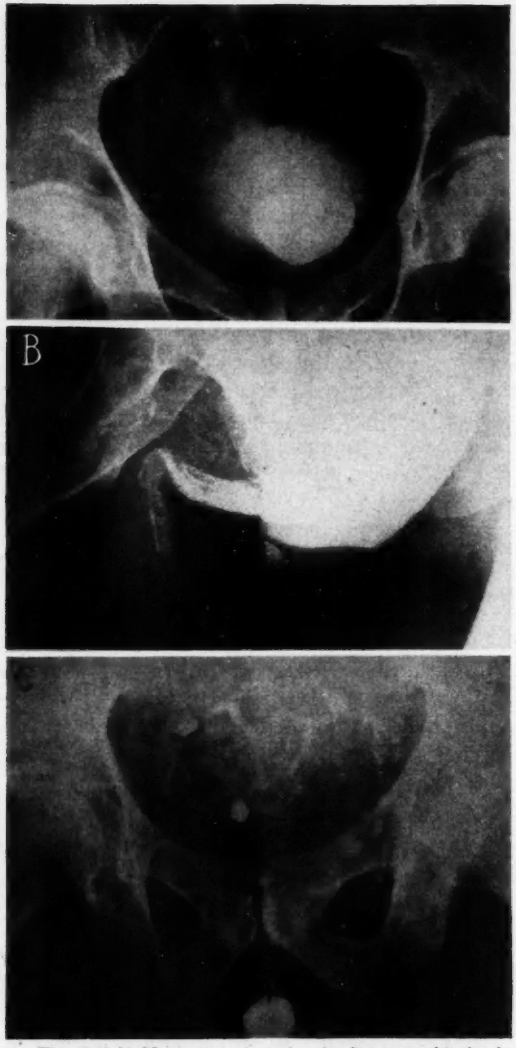

Fig. 3 *(A)* No venous invasion is demonstrable by intravenous pyelography. *(B)* X-ray half-hour after completion of urethrogram. Lipiodol is still present in urethral channel, apparently within urethral tissues. *(C)* X-ray one hour after urethrography. Oil is shown in urethra (to be seen at bottom of film), as a droplet in bladder, as scattered blotches around pelvis, and filling two deep vessels of pelvis.

view of a series of urethrograms indicates that small degrees of venous invasion have occurred in my patients previous to the case which is reported herewith. It is not easy to determine, in the few instances in which such extraneous shadows are now noted, whether slight reactions to urethrography were due to this occurrence. The case to be described has warned me of the possibility of venous invasion during urethrography and medication of the urethra to such a degree that I shall take greater care in performing these procedures in the future.

CASE REPORT

J. J. H., a married man, aged forty-eight, was seen December 19, 1944. He gave no history of urinary trouble. He reported that he had been very tired for more than a year. His physician had given him pituitrin injections for some reason, and also injections of liver extract. X-rays of the gall bladder and gastrointestinal tract were negative. He had virus pneumonia about one year ago. The present illness began one month previously with diarrhea and frequency, which were soon followed by enuresis and urgency. The patient had never had a high temperature. He had been found to be sensitive to sulfa drugs, which produced rashes and fever. Since the onset of diarrhea and frequency, the urine had contained pus, which partly disappeared after sulfadiazine. The symptoms did not improve. For approximately ten days before admission the patient had been wearing a Cunningham clamp during the day to avoid soiling his clothes when urine escaped from the sudden onset of urgency.

The patient was a small, thin, nervous man. Aside from his pallor, he was in good general condition. The temperature was normal. There was some overdistention of the bladder, estimated at 3 to 4 ounces. The external genitalia were negative, except for slight irritation of the penis from the clamp. The prostate was not large or soft. The vesicles were large and full. The urine was slightly cloudy, concentrated, contained no albumin or sugar, and the sediment consisted of blood and pus in small amounts. A single attempt at catheterization with an 18 F. soft rubber catheter met with an obstruction at the external sphincter, and passage to that point caused some bleeding. Culture of the voided urine showed Staphylococcus aureus. Guinea pigs were negative.

An intravenous pyelogram (Fig. 3, *A*) was described as follows:

"Film of the abdomen shows marked calcification of the costal cartilages. The ribs are sloping. The kidneys are fairly well shown. There is quite a bit of gas in the colon. There are no shadows visualized in the urinary tract or gall bladder area. There are no calcified glands. There are a few shadows low in the pelvis which I interpret as phleboliths.

"Following injection of the dye, on the five-minute film there is good

filling of the calyces, infundibula, and pelves. The best filling is seen on the ten-minute film. The calyces on the right are better filled than on the left, but the left side is somewhat obscured by gas and fecal matter in the colon. On the right the ureter makes nearly a right angle with the kidney pelvis. The ureters are somewhat tortuous, but are not otherwise remarkable. The kidneys begin to empty on the forty-five minute film. On the sixty-minute film there is quite a bit of dye in the calyces and pelves, more on the right than the left. The bladder begins to fill on the five-minute film and shows increased filling. On the sixty-minute film the bladder outline is rather small and appears to be hypertonic, it looks as if there is a rather large diverticulum on the posterior aspect of the bladder, towards its inferior surface, as there is an area of increased density here. In the voiding film there is a rather large residual containing the dense shadow which I think is a large diverticulum. There is some tendency to dilatation of the lower ends of the ureters just proximal to the bladder.

"Conclusions: There is marked calcification of the costal cartilages and quite a bit of gas and fecal matter in the colon. There are no shadows visualized in the urinary tract. There are several shadows low in the pelvis which I believe are phleboliths. One or two of these shadows are rather close to the lower end of the left ureter. The kidneys appear to function fairly well, but there is some delay in emptying, especially of the right pelvis which makes a sharp angle with the upper end of the ureter. The bladder appears to be hypertonic and rather small. I believe a large diverticulum of the bladder is present. There is a large amount of residual urine. The posterior urethra appears to be elongated suggesting an enlarged prostate."

Five days later urethrography was done with lipiodol, 20 c.c. being injected (Fig. 3, *B*). There was no discomfort occasioned by the injection and no bleeding produced. The films showed a marked dilatation of the posterior portion of the anterior urethra. The margins of the urethra were irregular and there was some extravasation of the oil into the tissues around both the anterior and posterior urethra. Very little of the oil flowed back into the bladder. There was also some of the oil seen in the vesical veins. There was still quite a bit of the oil sticking along the dilated portion of the urethra (Fig. 3, *C*).

As soon as the nature of the unusual urinary tract findings and vein invasion was manifest, the patient was placed in hospital, kept in bed, put on forced fluids and given hot sitz-baths twice daily. Voiding was possible, especially after the baths, but the residual urine lasted for about three weeks. At the end of five weeks he left the hospital in good condition, without percussable residual urine, and comfortable. The urine contained a few white blood cells, but no blood. Culture of the voided urine yielded non-hemolytic streptococci and staphylococci.

By February, 1945, he voided a small stream when active, but it was of good force after he relaxed in a hot bath. Sandalwood oil gave him some relief from the urgency but produced rashes. He continued to

have nocturia once, but often urine would escape before the desire to void awakened him. He appeared to empty his bladder completely. The urine had become clear. All local and abdominal soreness was gone. Bowel action was excellent. At this time a 18 F. bougie was passed easily. Some grating sensation was felt in the prostatic urethra. After the dilatation the enuresis disappeared.

By March 26, 1945, the grating sensation in the prostatic urethra had

Fig. 4. Urethrogram unaccompanied by venous invasion made one year later. Urethrogram is normal except for fully dilated structure of bulbous portion of urethra.

disappeared and the urethra had been dilated to 27 F. easily. The symptoms of frequency and urgency had disappeared and no further bed-wetting occurred.

In May, 1946, intravenous pyelography and urethrography were done. There was no evidence of venous invasion from this procedure,

and no reaction. Stricture of the bulbous urethra was demonstrated. By passing a No. 27 bougie, it was found to be a fully dilated stricture. The urine was negative and all symptoms had disappeared. He considered himself to be well. The x-rays were described as follows:

"Films of the chest: The apex of the heart is on a level with the sixth interspace anteriorly. The transverse diameter of the heart is 12.3 cm. as compared with the internal diameter of the chest, which is 30 cm. The great blood vessels are not remarkable. The trachea is in the midline. There is marked accentuation of the normal dorsal curve, with sloping ribs. There is just slight coarsening of the normal lung markings, but no parenchymal involvement. Conclusions: The size of the heart is within normal limits. There is no x-ray evidence of active tuberculosis; would consider the heart and lungs within normal limits.

"The urethrogram shows that the lipiodol flowed back into the bladder (Fig. 4). There appears to be a constricted area just near the cut-off muscle which is suggestive of a stricture. The column of lipiodol in the anterior urethra is somewhat wavy along its margins, suggesting a low grade inflammatory process.

"Film of the abdomen shows no shadows in the urinary tract or in the gall bladder area. There are no calcified glands. Low in the pelvis there are a few shadows which I think are phleboliths.

"On the five-minute film following injection of the dye there is fairly good filling of the calyces, infundibula and pelves. The left kidney is somewhat obscured by gas in the colon. The kidneys appear to be in position and regular. The ureters are not remarkable except they appear to be slightly tortuous. On the sixty-minute film the kidneys are nearly empty. The bladder begins to fill on the five-minute film and shows increased filling. On the sixty-minute film the bladder is rather small and hypertonic; the margins of the bladder are wavy. The posterior urethra appears to be somewhat elongated. On the voiding film there is a small trace of the oil or dye in the bladder. Conclusions: The kidneys appear to be functioning well. The ureters are not remarkable except slightly tortuous. The bladder is hypertonic and and rather small. The posterior urethra appears slightly elongated suggesting an enlarged prostate."

CONCLUSIONS

From a summary of the few cases of venous invasion from urethrography which have been reported, from experience with the patient here described, and from studies of the venous plexuses in the genitalia, prostate, bladder and pelvic regions by injection methods, I conclude that:

Urologists may with profit recognize the readiness with which invasion of the venous systems of the genito-urinary organs and the plexuses of the pelvis takes place.

Venous invasion from urethrography, while appearing to be of infrequent occurrence, may, through more adequate sampling of films, be found to be of clinical significance, in explaining post-examination reactions.

From analysis of reported cases, death resulted in four of twenty-seven cases of venous invasion.

The phenomenon appears to be most likely to result when urethrography is done on patients with acute urethritis, after injury, after instrumentation of the urethra, and when undue force is applied during injection.

Venous invasion, almost certainly, occurs through pressure applied through voiding against obstruction in recently traumatized urethral channels.

Symptoms of pain or systemic reactions do not always occur where venous invasion is taking place. No harm at all may result.

Deaths from fat embolism, where oily media are used, may be almost instantaneous, or delayed a very few days. Clinical evidence of injury is dependent on the region in which the embolism occurs.

Oily media, when they reach the veins or lodge in the tissue such as lungs, disappear slowly in weeks or months. They may be bacteria-laden from infected urine.

Thorium should not be used for urethrography since it is a tissue irritant and remains permanently.

There is need for a soluble yet viscid medium for urethrography.

99 Commonwealth Ave., Boston, Mass.

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SUCCESSFUL HETEROLOGOUS TRANSPLANTATION OF CARCINOMA OF THE HUMAN MALE URETHRA

REPORT OF TWO CASES

CLYDE L. DEMING, M.D., MICHAEL S. HOVENANIAN, M.D., and HARRY S. N. GREENE, M.D.

From the Department of Surgery, Section of Urology, and the Department of Pathology, Yale University School of Medicine, and the New Haven Hospital, New Haven, Conn.

The selective ability of cancer to survive and to grow upon heterologous transfer offers a ready means of differentiation from other growths possessing a morphological or clinical resemblance. In an attempt to classify tumors of the genito-urinary tract with respect to this ability a series of investigations has been instituted. The present paper describes the results obtained on transfer of two growths of a human male urethra and a clinical and pathological correlation of these growths.

MATERIALS AND METHODS

Guinea pigs were employed as alien hosts in the experiments to be described, and the anterior chamber of the eye was used as an inoculation site. The technique in an anterior chamber transfer is extremely simple. The chamber is opened close to the superior border of the corneo-scleral junction by means of a small incision with a double-edged cataract knife and a minute amount of fluid allowed to escape. A fragment of tissue measuring approximately 0.5 mm. in diameter is introduced by means of a trocar.

CASE REPORTS

Case 1.—M. F., N. H. H. No. B 44876, a forty-two-year-old white man, was admitted to the New Haven Hospital on May 13, 1943, complaining of frequency and bloody urine. He gave a five-month history of increasing frequency, difficulty in starting and a narrowing of the stream, and a painless priapism. He had lost 36 pounds in weight during the year. For many years the patient had suffered from "bronchitic asthma," but recently he had had some dyspnea and orthopnea. There

Acknowledgment: This work has been supported by a grant from the Connecticut Cancer Society, Incorporated, and appreciation for this aid is hereby expressed.

was no history of gonorrhea. The family history was free from cancer stigma.

Physical examination showed the patient to be fairly well developed but poorly nourished. The head, ears, nose, throat, and mouth were normal except for marked dental caries. The lungs were resonant to percussion, but there were diffiuse coarse wheezes throughout with fine rales at the bases. The heart was normal. The bladder was distended almost to the umbilicus. The penis was in a constant semi-erect position

Fig. 1. Case 1. Photograph of patients shows semi-erection in proximal half of penis and distended superficial veins.

(Fig. 1). The proximal halves of each corpora cavernosa were hard, irregular and nodular. The lymph glands in the groins, especially the right, were enlarged to 1 cm. in diameter, hard and discrete. The left thigh showed some weakness of the muscles but there were no sensory changes. Digital examination of the rectum revealed a benign enlargement of the prostate, one and one-half times normal size.

Laboratory findings: red blood cell count, 4.5 million; hemoglobin, 14 gm.; white blood cells, 9,000, with a normal differential. The urine showed 1 plus albumin and many pus cells and many cocci. Blood Kahn test was negative; nonprotein nitrogen was 28 mg. per cent.

When attempts to catheterize the bladder to relieve distention proved unsuccessful, a suprapubic cystostomy was performed under spinal anesthesia on May 14, 1943. At the same time a biopsy of a subcutaneous nodule from the penis and of an inguinal node was obtained. At operation the interior of the bladder did not reveal any tumor, but a subsequent urethrogram showed marked irregularity and narrowing of the urethra in the bulbar portion. A series of x-rays revealed diffuse pulmonary and bony metastases (Fig. 2).

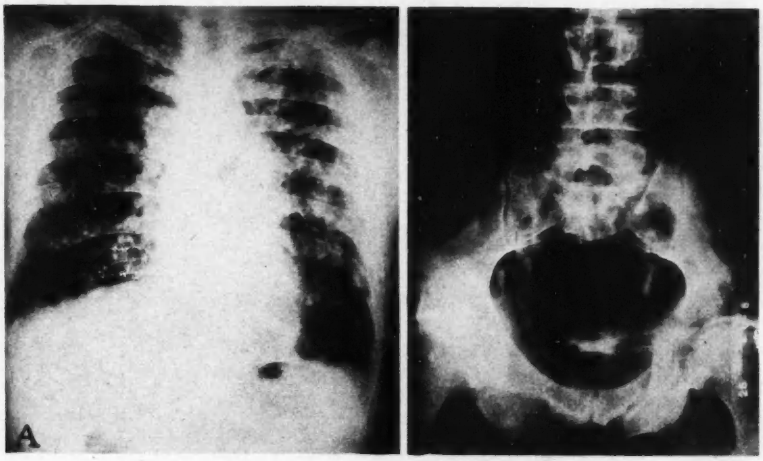

Fig. 2. *(A)* X-ray of lungs shows diffuse pulmonary metastases throughout both lung fields. *(B)* Photograph of x-ray of pelvis and lumbar region, demonstrates bony metastases to pelvis, osteolytic type, indicated by arrows.

The patient remained in the hospital twenty-nine days. During his stay, considerable pain developed in the left hip and thigh. In view of the metastatic nodes, weight loss and bone and lung lesions, it was believed that the tumor was too extensive locally and too widely disseminated for surgical removal; consequently palliative x-ray to the thigh and pelvis was given with marked relief of pain. He was discharged on January 12, 1943, because his family wished to have him home for terminal care. He died the same day. No post-mortem examination was obtained.

Microscopic study of the biopsy of the subcutaneous nodule of the penis and of the inguinal node showed numerous clumps and strands of cells with vesicular nuclei and a faint-staining cytoplasm. In some areas the cells were arranged in an epidermoid fashion, while in others they formed abortive glands and acini. A marked desmoplastic reaction surrounded the epithelial cells. The section of the inguinal node showed

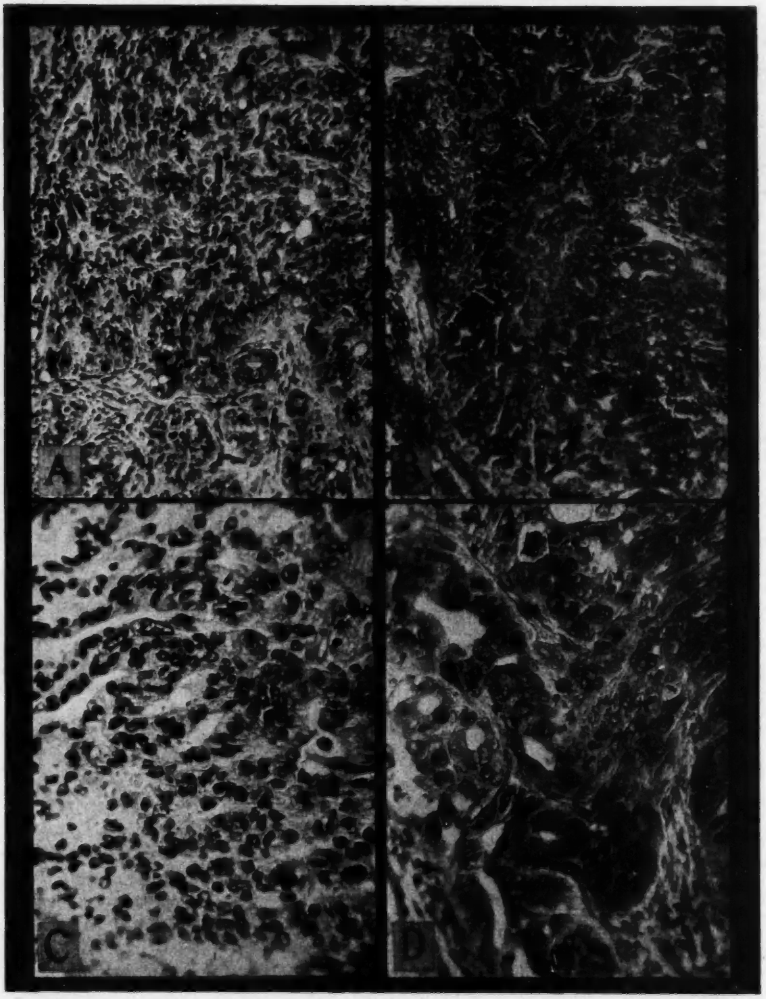

Fig. 3. *(A)* Photomicrograph (× 165) of biopsy of lymph node shows epidermoid character of tumor and attempt at gland and acini formation. *(B)* photo micrograph (× 125) of transplant to guinea pig eye after 81 days. Note epidermoid character and attempt at gland and acini formation similar to *A*. *(C)* Photomicrocraph (× 335). High power of original tumor. Many mitotic figures are present. Attempt at gland formation is evident. *(D)* Photomicrograph (× 425) of transplant. Gland formation is present. Tumor is similar to human cancer.

almost complete replacement of the normal tissue by tumor tissue. A section from the lymph node was transplanted into the anterior chamber of the eye of the guinea pig. The histopathological diagnosis was adenoacanthoma of the urethra. (Fig. 3).

Case 2.—C. P., N. H. H. No. B 49214, a sixty-two-year-old white man, was admitted to the New Haven Hospital October 14, 1943, complaining of pain and swelling of the penis. For about three months he had noticed increased difficulty in voiding, and he had had bouts of

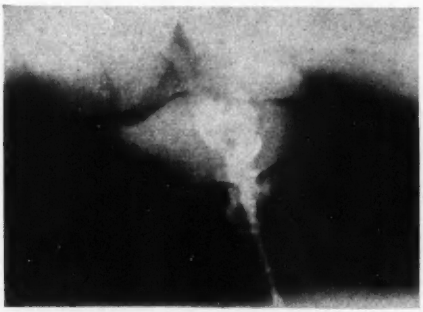

Fig. 4. Case 2. Photograph of urethrogram shows extravasation of dye about urethra and fistula. Note "puddling" of dye.

afternoon fever. His urine had become progressively cloudy and the foreskin swollen. Three weeks before entry, at another hospital, a circumcision had been performed, following which an abscess of the foreskin and a urethral fistula just posterior to the frenum had developed. He had lost 30 pounds during the year. There was no history of venereal disease. Past history and family history were negative. Physical examination revealed a well developed and nourished elderly man who showed evidence of recent weight loss. The abdomen was normal except for bilateral enlarged, tender inguinal glands. The penis was two or three times normal size with brawny, indurated and wrinkled skin. Beneath the frenum there was a discharging fistula. Rectal examination did not reveal any disease in the prostate, seminal vesicles, posterior wall of the bladder and rectum.

Laboratory findings: red blood cell count, 3.9 million; hemoglobin, 12 gm.; white blood count, 8700, with a normal differential. The urine showed 1 plus albumin and was loaded with pus, red blood cells, bacilli and cocci. Blood Kahn test was negative. The nonprotein nitrogen was 25 mg. per cent.

Skiodan injection of the urethra and fistula showed a jagged, prolonged drainage tract below the frenum (Fig. 4). The patient was placed on sulfadiazine by mouth, and the next day incision and drain-

age of the fistulous tract was performed under sodium pentothal anesthesia. Postoperatively the patient did well, but the incised area and fistula continued to drain. He was discharged three weeks after operation, to be followed in the out-patient clinic.

On February 3, 1944, the patient was re-admitted because of persistent pain and swelling of the penis. A preoperative diagnosis of carcinoma of the urethra was made, and on February 4, 1944, under pentothal anesthesia, the penis was amputated (Fig. 5) and the urethra

Fig. 5 *(A)* Photograph of surgical specimen of penis, dorsal aspect. *(B)* Photograph of surgical specimen with urethra open, show localized tumor formation in anterior portion.

transplanted into the perineum. The patient did well postoperatively and was discharged after seventeen days.

Grossly, the urethra showed an ulcerated tumor 2 by 1 cm. Microscopic section of the penis revealed a solid infiltrating tumor, characterized by groups of cells, epidermoid in appearance, with vesicular nuclei and a light-staining cytoplasm. In some areas there was a definite tendency towards "pearl" formation. Many mitotic figures were present. The pathological diagnosis was epidermoid carcinoma of the urethra (Fig. 6). A section of the gross tumor was utilized for guinea pig transfer.

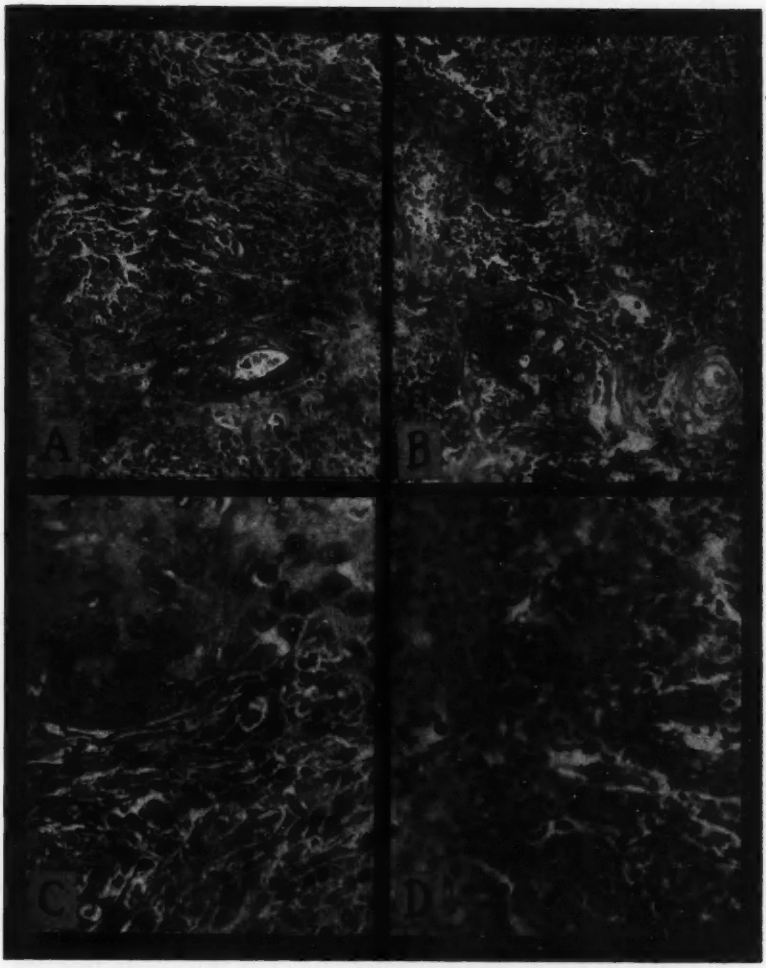

Fig. 6. *(A)* Photomicrograph (× 130), section of tumor of urethra, shows epithelioid nature of carcinoma. *(B)* Photomicrograph (× 130) of guinea pig transplant after forty-three days. Similarity to human cancer is apparent. There is a marked inflammatory reaction to confines of tumor. *(C)* Photomicrograph (× 300) of cancer of urethra shows mitoses and marked epidermoid nature and attempt at pearl formation. *(D)* Photomicrograph (× 300). High power of guinea pig transfer.

On May 15, 1944, the patient was re-admitted to the hospital because of enlargement of glands of both groins. Block dissection and excision of all the glands in both groins down to the femoral and external iliac vessels was done, and microscopic section revealed almost total replacement of the lymph tissue by cancer cells. After nine days hospitalization, during which no other metastatic foci were found by x-ray, the patient was discharged. He was followed in the tumor clinic for some time; considerable pain and swelling developed in the left leg. At another hospital he was treated for ischiorectal abscess and thrombophlebitis of the left leg. He died September 1, 1945, about twenty-six months after the onset of symptoms. Prior to death it was noted that he had a recurrence of the epidermoid cancer in the remaining urethra and in the bony pelvis. An autopsy was refused.

RESULTS AND CONCLUSIONS

Using both male and female guinea pigs as alien hosts, heterologous transfer was successfully carried out. In the first case the cancer originated in the posterior portion of the anterior urethra, and the section used for transfer was derived from its metastatic inguinal lymph node. Ten animals were inoculated, six male and four female, and a single "take" resulted. This animal, a male, was sacrificed on the eighty-first day following inoculation, at which time the anterior chamber of the eye was two-thirds filled by tumor. In the second case, the cancer originated in the anterior portion of the anterior urethra, and a section of the cancer from that area was transplanted. Four animals, all male guinea pigs, were selected as alien hosts, and again a single "take" resulted. The animal with the successful "take" was sacrificed after forty-three days, at which time the anterior chamber was one-half filled by tumor.

Morphologically the transplants resembled the original tumor in every respect. In the case of the adenoacanthoma both epidermoid and adenoid architecture was present in the transplant and, in the second, the epidermoid structure of the transplant reflected that found in the original tumor.

Cancers of the urethra like other malignant growths in man are transplantable heterologously. The subsequent history of the two cases in question bears out the previous suggestion that only those tumors capable of heterologous transfer are true cancers. Growth of transplant in alien hosts reflects the morphological character of the growth in the original human host.

SUMMARY

Two cases of successful heterologous transplantation of carcinoma of the human male urethra are presented.

Morphology of the transplanted cancer in the guinea pig reflected morphology in the human host.

Subsequent clinical history bears out results of biological test for true cancer.

DISCUSSION

DR. BENJAMIN S. BARRINGER (New York, N. Y.): I just want to mention two cases. The first, of bilateral teratoma of testes, is extraordinarily rare, as we all know, and the second is a case of chorionepithelioma, with survival for well over five years. I think Dr. Nesbit had a patient with chorionepithelioma who survived for over five years.

I wanted to ask Dr. Taylor if he had heard of any other case of chorionepithelioma with survival for well over five years.

DR. WILLIAM P. HERBST, JR. (Washington, D. C.): The abstract of Dr. Taylor's presentation and Dr. Hovenanian's presentation revolve about the problem of whether the factor is androgen or estrogen predominantly.

Several years ago Dr. McClelland presented some very interesting cases of testicular tumors in which subsequent castration resulted in a favorable clinical retardation for some time. The patient in which Dr. Taylor removed the other testicle seemed to do pretty well. That seemed most significant. Then on top of this, there are the guinea pigs, a male guinea pig and a female guinea pig, with growth taking place in both of them. The answer to the question, therefore, is very definitely inconclusive.

DR. JOHN K. ORMOND (Detroit, Mich.): I wish to say a word in connection with Dr. Taylor's presentation. We have had occasion recently to review all of our testicular tumors, only about thirty in number, and we have had only two cases of chorionepithelioma, and both patients are still living after two and three years.

I personally haven't seen any recurrence of carcinoma of the testicle after four years. Apparently if our patients live four years, they go on living.

Another thing that has struck us, which I suppose isn't new at all, is the influence of age on the survival. Of the patients who were under thirty, two-thirds are dead, and of the patients that were over thirty, two-thirds are living.

DR. ALEXANDER R. STEVENS (New York, N. Y.): I would like to ask Dr. Crabtree to present his advantage in using these oily mixtures and the nondissoluble things over the iodides.

DR. JOHN A. TAYLOR (New York, N. Y.): I thank the men for their discussion.

I didn't make an exhaustive study of the literature, but I did not find any report of a five-year survival.

DR. JAMES C. MCCLELLAND (Toronto, Ontario): I haven't anything to add to what I said, but I intended to speak in regard to Dr. Taylor's paper. Some two years ago I had an additional patient with a testicular tumor who was greatly benefited by removing the remaining testicle. He was a major in the Canadian Army, forty-two years of age. He came in with multiple secondary lesions in both sides of his chest. His voice was quite hoarse, and there were a good many secondary lesions in the hilus of the lung on the left side. He was not in good shape. We removed the remaining testicle, and within four days his voice had improved considerably. An x-ray taken twenty-eight days following the orchidectomy showed a marked decrease in secondary lesions in both lungs. That was about October, and he was followed through until the following April. The secondary lesions didn't disappear completely, but there was a marked decrease in size. Then after a period, March or April, they increased again in size, and he died in two or three months, in the early summer.

There is no doubt but that he was greatly benefited by our removing the other testicle.

I have had three further patients who were very far advanced with secondary lesions in the lungs, in whom the second testicles were removed, and they were not benefited.

DR. E. GRANVILLE CRABTREE (Boston, Mass.): I think you will have gathered from my paper that it was essentially an historical report showing the possibilities of dissemination of drugs in general. I realize that a certain amount of viscosity in fluids used for urethrography makes for better pictures than are obtained with thin fluids. I believe all of us are using skiodan for certain phases of our urethrography, and of course other drugs are used in the urethra for anesthesia and treatment. Essentially my paper is historical, and not advice.

BILATERAL HYPERNEPHROMA

CASE REPORT

FEDOR L. SENGER, M.D., JOHN J. BOTTONE, M.D., and GEORGE E. MURRAY, M.D.

From the Department of Urology, Long Island College Hospital, Brooklyn, N. Y.

The rarity of occurrence of bilateral renal neoplasms makes all such cases worthy of report. The authors wish to report a case of bilateral hypernephroma which was diagnosed and the diagnosis confirmed by tissue study of the tumors during life. This case also presents the unusual occurrence of a metastatic lesion appearing in the thyroid gland.

REVIEW OF LITERATURE

After an exhaustive search of the literature we have been able to find sixteen apparently authentic instances of primary bilateral renal carcinomas. Küster reported one case of bilateral hypernephroma in 1902. In 1903, Albarran and Imbert reported four cases of bilateral epithelial carcinomas. Chute (1910) published the first case of bilateral hypernephroma to appear in the American literature. This was followed by case reports of Weber in 1915, Hunt in 1927, Sanford in 1931, who reported a base of bilateral transitional cell carcinoma, Spengler and Bohrod, who reported two cases in 1935, a Mallory case report in 1936, Forsythe in 1942, Beilin and Neiman in 1942, and Melicow, in 1944, who reported two cases.

There are other reports in the literature of bilateral renal neoplasms in which the diagnosis was based on clinical and roentgenological evidence without being supported by tissue study, or in which the lesion in the second kidney was thought to be metastatic. These have been purposely omitted from this report.

Lubarsch records eight instances of renal neoplasms that metastasized to the thyroid gland.

CASE REPORT

K. L., L.I.C.H. No. 2100, a twenty-seven-year-old housewife, entered the Long Island College Hospital on April 6, 1933, complaining of painless hematuria for three days. She had felt well until the onset

of this frank hematuria. Slight dysuria was noticed on the day of admission. There was no history of abdominal or loin pain, chills or fever, nor had any weight loss been noticed. Her last menstrual period had finished two weeks prior to hospitalization. Physical examination was entirely negative. The laboratory findings revealed grossly bloody urine but were otherwise negative.

Hematuria had ceased the following morning, and cystoscopy revealed a freely movable small blood clot in the bladder. Meatoscopy showed grossly clear urine being emitted from the ureteral orifices which were normal in appearance. Bilateral ureteral catheterization was easily done and urine from both kidneys revealed 3 to 4 red blood cells. Bilateral pyelography was done; the roentgenologist's report is submitted in detail because the original films were discarded. "Examination of the KUB tract with opaque ureteral catheters in both sides, extending to the second lumbar vertebra on the right, to the first lumbar vertebra on the left side; right kidney shadow is normal in position and contour; no opaque calculus. Left kidney shadow is distinctly outlined, apparently not enlarged; no opaque calculus. Ureteral regions down to the level of the ischial spines appear negative. Lower ureteral and bladder regions not seen. Bilateral pyelography with the right catheter at the level of the fifth lumbar vertebra and the left catheter at the level of the second sacral segment. Film shows gross motion and detail is not entirely satisfactory. However, there is no apparent pathology noted in either kidney pelvis. There appears to be a slight degree of kinking and ptosis of the right ureteropelvic junction and slight relative widening of the right ureter. Left ureter appears normal. Ureteropelvic junction is indistinctly outlined. There is no kink noted at this level. Bladder region is incompletely seen. Conclusions: Probably negative except for some ptosis of the right kidney."

The patient was discharged the following day and advised to return in three months for a re-examination.

She was next seen on March 10, 1941, eight years after her first admission, at which time she was readmitted to the hospital complaining of a painless swelling in her left upper abdomen. She had noticed a progressive weight loss of 25 pounds during the past three years, and weakness and pallor for the past three months. The patient had first noticed this "lump" on Thanksgiving Day, 1940. The mass had grown progressively larger, but at no time had she noticed any pain or hematuria. Positive findings on physical examination were a smooth, plum-sized mass in the region of the itshmus of the thyroid gland, and a firm, easily ballotable mass in the left upper abdominal quadrant which was fairly mobile and moved slightly on respiration. The pertinent laboratory findings were hemoglobin 72 per cent, 10 to 15 white blood cells and an occasional red blood cell in her urine, and a basal metabolic rate of —2.

Cystoscopy revealed a normal bladder; both ureters were easily catheterized. Phenosulphonphthalein excretion was normal from the right kidney with good concentration; none appeared from the left side after

ten minutes. Bilateral pyelography disclosed an essentially normal right kidney and ureter; the left ureter was seen to deviate to the midline and the outline of the left kidney was obscured, the left pyelogram showd distortion of the pelvis with spider leg formation (Fig. 1). A diagnosis of left kidney tumor was made. A roentgenogram of the chest was negative.

A left nephrectomy was performed on March 25, 1941, through a loin incision. The kidney was found to be extensively involved with a

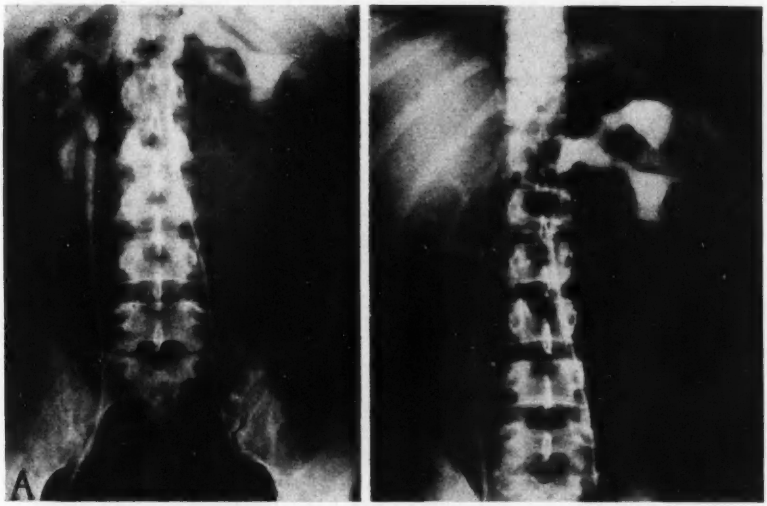

Fig. 1. *(A)* Right retrograde pyelogram (February 20, 1941) shows normal outline of right kidney, pelvis and ureter. *(B)* Left retrograde pyelogram (same date) shows left kidney tumor mass with "spider leg" formation of pelvis and deviation of ureter toward midline.

tumor, which was removed without undue difficulty. There was no involvement of the pedicle noted at operation.

The pathologic report reads: "The gross specimen consists of a nodular oval soft mass which measures 23 by 13 by 11 cm. and weighs 1300 gm. It is surrounded by dense fibrous tissue through which at one pole protrudes a mass of renal tissue measuring 6 by 5.5 by 3 cm. On section the mass is found to consist of soft, yellow, hemorrhagic tissue containing numerous cystic spaces filled with fluid and clotted blood. Although encapsulated around the periphery, it is invading the remnant of kidney, and masses of soft, yellow, tumor tissue lie in the pelvis. The ureter cannot be found. The cut surface has a bizarre, extremely varied appearance. Soft yellow tissue alternates with large and small cysts,

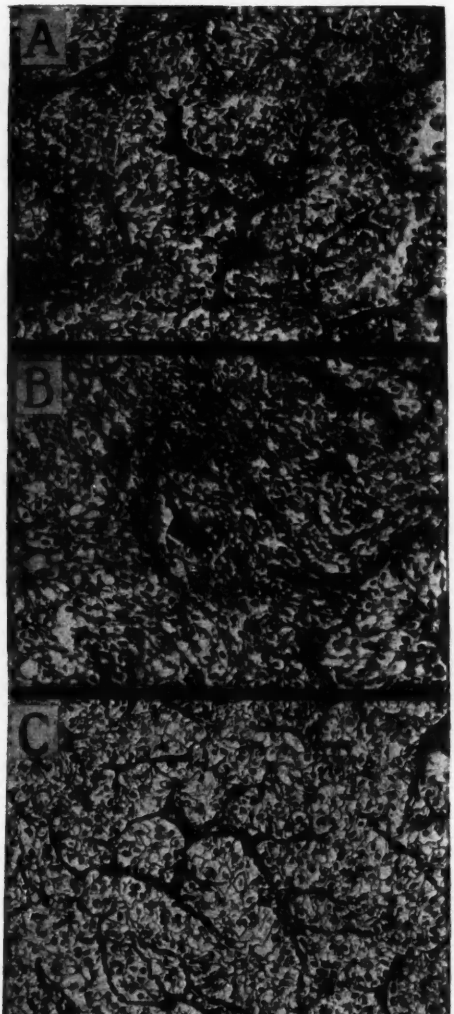

Fig. 2. *(A)* Left tumor. × 150. Note large vesicular cells with tubular formations. *(B)* Biopsy from right tumor. × 150. Note large vesicular cells with clumping and small lumina formation. *(C)* Biopsy from thyroid gland. × 150. Note marked similarity between this and *A* and *B*.

firm greyish-brown fibrous tissue and green necrotic debris. Microscopic description: The tumor varies somewhat in appearance from place to place. Large areas are necrotic and hemorrhagic and in these no cell detail can be made out. Where the cells are viable, however, they are seen to be forming small tubules. They are large pale vesicular cells and frequently no cytoplasm whatsoever can be made out. They have round or oval nuclei containing diffusely scattered chromatin. Many of the tubules are filled with red blood cells. At its junction with the kidney there is everywhere a well-defined fibrous capsule. The renal tissue does not appear to be invaded by the tumor but in the neighboring kidney the tubules are compressed, atrophic and surrounded by fibrous tissue.

"Diagnosis: hypernephroma" (Fig. 2, *A*).

An uneventful convalescence ensued. The patient was discharged April 23, 1941. She reported to the Urological Clinic at intervals until November, 1942, at which time she complained of three days of painless hematuria. Cystoscopy and retrograde pyelography at this time showed an irregular outline of the lower pole of the remaining kidney with some elongation of the lower calyceal group. A tentative diagnosis of right renal tumor was made (Fig. 3, *A*).

On February 10, 1943, she was admitted to the hospital complaining of dull right flank pain and nausea. Profuse painless hematuria had been present for the preceding two days and she had not voided for twelve hours prior to admission. At this time the patient appeared acutely ill and presented marked pallor. A tender, mobile mass was felt in the right upper quadrant of her abdomen. The nodule in her thyroid gland was unchanged from the previous admission. The hemoglobin was 55 per cent. Bladder catheterization obtained only a few drops of blood.

Intravenous fluids were administered but the anuric state was maintained for thirty-six hours, at which time cystoscopy was performed. In attempting to catheterize the right ureter a worm-like clot was evacuated, after which the catheter passed with ease, and approximately 80 c.c. bloody urine was evacuated from the renal pelvis. The pelvis was irrigated with warm saline every two hours for about twelve hours, at which time the catheter was passed spontaneously. On February 16, 1943, intravenous urography revealed an enlarged right kidney and definite tumor contour in the pyelogram (Fig 3, *B*).

It was decided to explore the kidney with the possibility of either resecting the tumor or implanting radon seeds to control the growth. On February 19, 1943, the kidney was exposed through the usual lumbar approach. The kidney was found to be involved throughout the lower and middle poles with a friable, yellow, tumor mass that measured approximately 6 cm. by 6 cm. A biopsy was taken, satisfactory hemostasis obtained and the kidney was replaced in the wound.

The pathologic report reads: "The gross specimen is an irregular mass of extremely soft, friable and hemorrhagic yellow tissue. It meas-

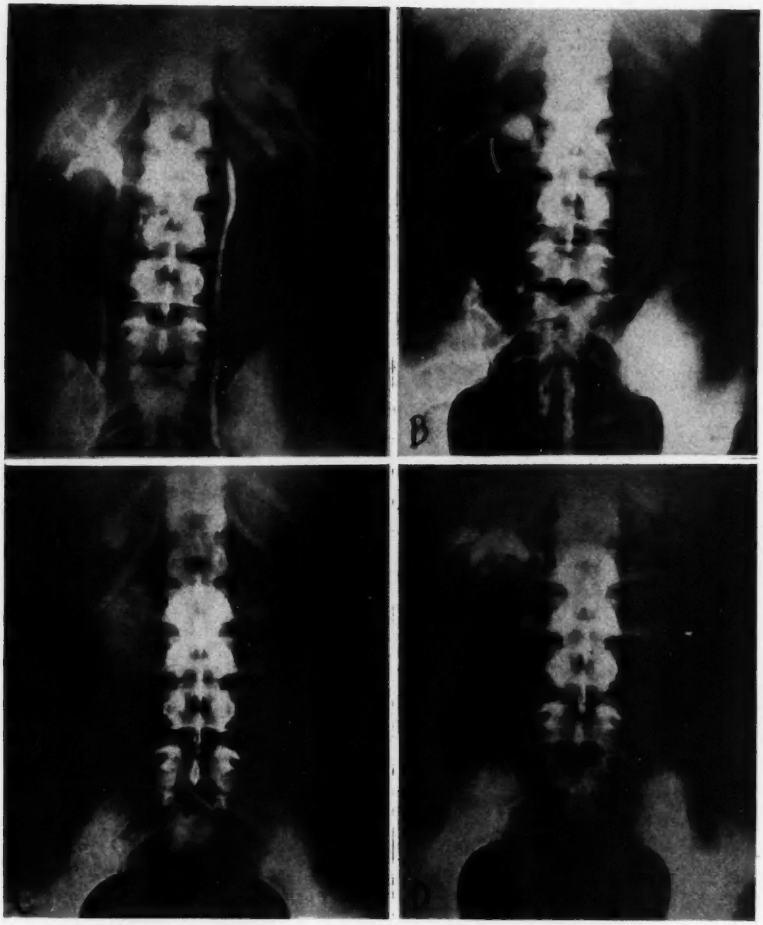

Fig. 3. *(A)* Right retrograde pyelogram (November 20, 1942). Note irregular dilatation of pelvis with elevation of lower major calyx. Also note appearance of tumor mass in lower pole. *(B)* Intravenous pyelogram (February 16, 1943). Note lower pole tumor mass with marked elevation and elongation of lower major calyx. *(C)* Intravenous pyelogram (May 11, 1943) shows distortion of pelvis and calyces with ureteral deviation to midline and presence of a large tumor mass in lower pole. *(D)* Intravenous pyelogram (April 7, 1944). Note further distortion of pelvis and calyces and increased size of lower pole tumor mass.

ures 1.5 by 1 by 1 cm. Microscopic description: The section consists of epithelial tumor tissue in which there is much hemorrhage. The epithelial cells are arranged in small clumps separated by delicate strands of fibrous stroma. In some of the clumps there are small lumina. The tumor cells are large but their cytoplasm is markedly vesicular. Their nuclei are irregularly rounded or oval and contain a moderate amount of chromatin. Mitotic figures are not encountered but anaplasia is considerable. A large part of the tumor is completely necrotic and consists only of glandular acidophilic debris containing fragmented nuclei and numerous red blood cells. Diagnosis: carcinoma of the kidney (hypernephroma)" (Fig. 2, *B*).

The patient made an uneventful recovery and was discharged on March 19, 1943, to the clinic, where deep roentgen therapy was administered to the tumor. Intravenous urography on May 17, 1943, and April 7, 1944, showed progression of the right renal tumor pattern (Fig. 3, *C* and *D*). A mass developed in the left operative scar; a biopsy taken May 10, 1943, showed tumor tissue identical in appearance to the kidney tumor that was removed.

The patient was not seen again until November 17, 1944, at which time she entered the hospital complaining of increase in the size of the nodule in her neck, dizziness and fainting spells. She had felt reasonably well except for easy fatigability and occasional pain in her right side. Physical examination at this time revealed a firmly fixed, nontender, orange sized mass in the region of her thyroid gland. There was a firmly fixed, nodular mass in the right upper quadrant of her abdomen which extended to the midline anteriorly, and below the level of her iliac crest. A small local regrowth was present in the left operative scar. Laboratory findings revealed hemoglobin of 35 per cent, 10 to 15 red blood cells and 10 to 15 white blood cells in her urine, basal metabolic rate —1, urea nitrogen 46 mg. per 100 c.c. blood. Intravenous urography showed markedly diminished function and a grossly distorted pelvis with a faint trace of dye appearing at the end of 60 minutes.

On December 13, 1944, the thyroid mass was explored and found to consist of necrotic tumor tissue from which a specimen was taken for pathological study. The report reads as follows: "The gross specimen is composed of two pieces of yellowsh white, moderately scarred tissue 2 cm. and 1 cm. in thickness. Microscopic description: The specimen is a malignant, glandular tumor apparently arising from kidney epithelium. There is an attempt to reproduce kidney tubules. There is moderate scarring, a rich blood supply and small areas of degeneration. Diagnosis: adenocarcinoma, kidney, metastatic to thyroid" (Fig. 2, *C*).

After two blood transfusions the patient was discharged on December 22, 1944. She has continued to feel rather weak but is able to do light housework.

TABLE I

Author	Sex	Age	Initial Symptom	Treatment	Duration Before Recurrence of Symptom	Secondary Symptoms	Treatment	Final Diagnosis
Beilin and Neimann	M	50	Hematuria	Left nephrectomy	5½ years	Hematuria	Supportive	Bilateral hypernephroma; no discernible metastases; no autopsy
Chute	M	62	12 years dysuria and hematuria	Laparatomy	Death in 5 days			Bilateral hypernephroma; metastases to bladder and intestine; no autopsy
Forsythe	M	62	3 years of painless hematuria	Cystotomy right nephrectomy	Death			Tumor thrombus pedicle and vena cava; autopsy
Hunt	M	65	10 mos. hematuria	Left nephrectomy showed hypernephroma	Death in 5 days			Right hypernephroma; autopsy
Mallory case	M	59	Left nephrectomy 13 yrs., back pain 5 mos.	Exploratory of parathyroid	Death in 5 days			Recurrent left hypernephroma; right hypernephroma; metastases to lungs and bones; autopsy
Sanford	M	56	2 mos. hematuria	Right nephrectomy showed transitional cell carcinoma	Death in 3 weeks			Left transitional cell carcinoma; no autopsy
Spengler and Bohrod	M	71	Hematuria 3 yrs.	Cystotomy	Death in 8 days			Bilateral hypernephroma; autopsy
Same	M	?	Weight loss and dizziness	Supportive	Death			Bilateral hypernephroma; metastases to liver, lungs and pancreas; autopsy
Weber	M	49	Uremic coma	Supportive	Death in 3 days			Bilateral hypernephroma; metastases to liver and lungs; autopsy
Senger, Bottone and Murray	F	27	Hematuria; 8 yrs. later loin mass	Left nephrectomy after appearance of mass	20 mos.	Hematuria	Biopsy and radiation	Bilateral hypernephroma; metastasis to thyroid; no autopsy; patient alive at writing

DISCUSSION

The subject of multiple neoplasms is of utmost interest to the pathologist as well as to the clinician. Multiple neoplasms are no longer held to be pathologic curiosities. The postulates of Bilroth that in order that neoplasms shall be considered multiple they shall be of different origin, shall present different pathologic structure and each shall produce its own metastases, are now recognized as being too confining. Major states that multiple identical malignancies may arise in the same organ, in the same system of organs, or in different organs, and that they need not produce metastases. Ewing believed that the occurrence of multiple neoplasms within a system are instances of multicentric growths due to the same etiological factor, and exemplify the tumor diathesis of the patient. When two tumors of different structure are found, it is obvious that they are of independent origin. However, when these tumors arise from identical tissue and are found to be of almost identical structure, proof of the independent origin of each on a basis of differences in their pathological appearance becomes impossible.

Although the patient is still alive and we cannot present an autopsy study, we believe that this case presents sufficient clinical and pathological data to allow us to compare it with the literature pertaining to the subject and to arrive at a justifiable assumption that these tumors were of independent origin. This case presents bilateral hypernephroma with the only discernible metastatic lesion found to be in the thyroid gland after repeated clinical and roentgenological examinations. The advancing slow growth of the left tumor without metastases to the lungs, long bones or skull make it highly improbable that it should metastasize to the remaining kidney. Furthermore, our serial pyelograms that show the gradual development of a tumor pattern in the solitary kidney further indicate the independent origin of the second tumor.

We have been able to find one case where the diagnosis of tumor in the remaining kidney has been confirmed during the life of the patient by tissue study.

We note that we have here the unusual occurrence of a metastatic lesion appearing in the thyroid gland. We find that this gland is the seat of an adenoma which is in keeping with Lubarsch's discussion of this unusual happening.

Table I summarizes the available data of the reported cases of bilateral primary renal carcinoma.

SUMMARY

A case of bilateral hypernephroid carcinoma is presented with pyelograms which show the progressive development of the tumor in the solitary kidney, and also a biopsy study of the tumor in the solitary kidney.

This is the first case of bilateral hypernephromata in a female, and the second case in which a biopsy has been obtained to prove tumor in the remaining kidney.

The literature has been reviewed and summarized to bring the total number of reported cases to seventeen.

144 Jaralemon St., Brooklyn, N. Y.

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THE SURGICAL TREATMENT OF POLYCYSTIC DISEASE OF THE KIDNEY

CASE REPORTS

AUSTIN I. DODSON, M.D.

From the Urological Services of St. Elizabeth's Hospital and St. Luke's Hospital, Richmond, Va.

In polycystic disease the destruction of renal tissue results from pressure exerted by the gradual increase in the size of congenital cysts interspersed throughout the kidney. Most patients with polycystic kidneys are beyond thirty years of age before the disease is recognized. Therefore, it is evident that the cysts grow slowly and many years are usually required for the disease to manifest itself clinically. Consequently, it seems logical to operate upon these patients as soon as the disease is recognized, excising a portion of the wall of the superficial cysts and aspirating as many as possible of those more deeply situated. From a review of the literature the attitude of those who discuss the subject is much more conservative. Although a few authors seem to favor the surgical treatment of polycystic disease of the kidneys, most of them consider the treatment largely medical and prefer to resort to surgical intervention only when there is obstruction, stone, infection, severe hemorrhage, or when pain becomes incapacitating. The principal objections to conservative operations in the treatment of polycystic kidneys are that fistula may result, infection may spread to the rest of the kidney, and the results are very uncertain. In the past I have followed these principles. Experience with two patients recently treated for polycystic kidneys causes me to question my former conservative attitude toward this disease.

CASE REPORTS

Case 1.—Mrs. J. T. C., thirty-six years of age, was admitted to the hospital on February 22, 1945, because of pain in the back, nausea and vomiting. She stated that she had had attacks of "kidney colic" since she was in high school. The attacks of pain were irregular in occurrence, from three or four months to two or three years apart. The pain rarely lasted more than twenty-four hours. The present attacks began about the first of February, were quite severe and accompanied by fever, nausea and vomiting. After a week of illness she was taken to a

hospital where catheters were inserted and left eight days for drainage. The symptoms were relieved and she was permitted to return home. Within a week there was a recurrence of the discomfort, accompanied by acute tenderness in the left lumbar area and left upper quadrant of the abdomen.

The patient was a well developed young woman who showed the effect of her three weeks' illness by considerable weight loss, pallor, and general weakness. Physical examination showed nothing of clinical in-

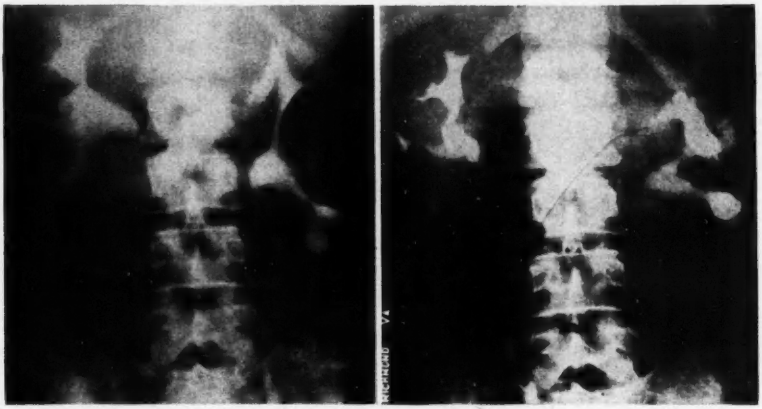

Fig. 1

terest except tenderness in both subcostal areas extending from the costovertebral angles well around over the upper abdomen. Tenderness on the left side was quite pronounced. There was general rigidity of all abdominal muscles which prevented satisfactory palpation of the kidneys, but fullness in both flank areas was quite evident.

Her temperature on admission was 100° F. and rose to 103° F. within a few hours. Pulse varied from 90 to 100. Red blood count was 3,700,000, hemoglobin 57, white blood cells 16,000, with 81 neutrophiles. The urine was acid, with specific gravity varying from 1.010 to 1.012, and contained a heavy trace of albumin and numerous red blood cells and pus cells. Phenolsulphonephthalein elimination was 35 per cent in two hours.

The bladder mucosa was moderately congested, and indigo carmine was eliminated in poor concentration from both kidneys in five minutes. Catheterized specimens from both kidneys contained many pus cells; positive cultures of E. coli were obtained. There was no residual urine in either kidney pelvis. X-ray examination was negative for stones. Pyelograms showed distortion of the pelves and calyces characteristic of cystic change (Fig. 1, *A*).

On February 28, 1945, the left kidney was operated upon. It was found to be markedly adherent throughout and the capsule was extremely thickened. In attempting to liberate the kidney a large abscess was found extending up toward the upper pole posteriorly. This was aspirated and drainage tubes were inserted. Further exploration disclosed several fairly large cysts filled with purulent material. These cysts were opened, the fluid was aspirated, and small tubes were inserted for drainage. The wound was closed in layers with interrupted sutures of No. 1 chromic catgut in the muscle and fascia and interrupted sutures of coarse cotton in the skin. The drainage tubes were brought out near the upper angle of the wound.

The patient seemed to be recovering satisfactorily until March 9, 1945, when there was an increase in discomfort in the left kidney area and a rise of temperature. This persisted with a maximum daily temperature of 103° F. until March 17 when the left kidney was again operated upon. Under ethylene anesthesia the old incision was opened and the kidney exposed. Several additional cysts were located under the surface of the kidney and were opened and drained. Small tubes were placed in these cystic areas and brought out near the upper angle of the wound for drainage. The wound was closed in layers, using No. 1 chromic catgut in the muscle and fascia and coarse cotton in the skin.

Following the second operation the discomfort in the left lumbar area was relieved, but the fever persisted with a maximum temperature of 102° F. It was then noticed that there was an increase in the pain and tenderness in the right lumbar area. The patient complained particularly that she could not lie on the right side. On March 27, 1945, the patient was again taken to the operating room and a right lumbar incision was made, exposing the right kidney which was not so adherent as the left. The kidney was liberated and brought into the wound. Several large cysts were opened and drained of purulent material. Small rubber tubes were placed in the depth of the cystic areas and brought out at the upper angle of the wound. The wound was closed in layers, using No. 1 chromic catgut in the muscle and fascia and coarse cotton in the skin.

Following this operation the patient gradually improved, her temperature becoming normal on April 5, forty-two days after admission. During her hospitalization she had three blood transfusions and at the time of her discharge from the hospital April 14, 1945, she was in fairly good condition, free of pain, and both wounds healed. The red blood cells numbered 3,160,000; hemoglobin 52 per cent. The urine still contained numerous pus cells and some albumin.

The patient was re-admitted for a check-up on May 29, 1945. This time the red blood cells numbered 3,350,000; hemoglobin 64 per cent; white blood cells 14,800; neutrophiles 88 per cent. The urine contained 15 to 20 pus cells per high power field and a trace of albumin; specific gravity was 1.011. There were 12 to 15 white blood cells from the right kidney and a very few from the left. Pyelograms indicated relief of pressure on the calyces (Fig. 1, *B*). The total phenolsulphonepthalein

elimination was 55 per cent, 10 per cent in the first half hour, 30 per cent in the second half hour, 10 per cent in the third half hour, and 5 per cent in the fourth half hour.

The patient returned to the office for observation in May, 1946. Her weight had returned to normal. Neither kidney was palpable and she stated she had been entirely comfortable for a period of twelve months. The specimen of urine from the bladder contained 10 to 15 pus cells per high power field, and indigo carmine was eliminated freely from both kidneys.

Case 2.—The second patient whose history will be given in less detail was a woman, aged sixty-four years, who was admitted to the hospital February 8, 1943, because of pain in the right lumbar area of twelve months' duration. The physical examination was essentially negative with the exception of a tender palpable mass in the right lumbar area. The red blood cells numbered 3,930,000; hemoglobin 78 per cent; white blood cells 3,200; neutrophiles 44 per cent, lymphocytes 52 per cent. The urine contained a few pus cells and rare hyaline casts. Phenolsulphonphthalein elimination on admission was 34 per cent the first half hour, 16 per cent the second half hour, 6 per cent the third, and 6 per cent the fourth, making a total of 62 per cent. X-ray examination was negative for stone. Pyelograms showed evidence of bilateral polycystic disease.

On February 9, 1943, the patient was operated upon. A right lumbar incision was made, exposing the right renal fossa. The right kidney was found to be cystic and very large. All of the cysts on the surface were incised and the contents evacuated. Part of the cyst wall was removed whenever possible. After the contents were drawn off, the kidney which had been reduced about half in size was returned to its bed. The fascia and fat were sutured to the lumbar muscles beneath the lower pole of the kidney. A rubber tissue drain was placed behind the kidney and brought out near the upper angle of the wound for drainage. The wound was closed in layers, using No. 1 chromic catgut in the muscle and fascia, and coarse cotton in the skin.

The patient made a satisfactory recovery from the operation. Phenolsulphonphthalein test on March 2, 1943, indicated a very slight diminution in the elimination of the dye, 25 per cent the first half hour, 20 per cent the second half hour, 8 per cent the third, and 5 per cent the fourth, making a total of 58 per cent. The patient left the hospital March 6, 1943, in good condition.

She was again seen in the hospital January 13, 1945, because of slight fever and pain in the right lumbar area. Examination disclosed mild pyelitis. The kidney pelvis was irrigated with normal salt solution and the patient made a prompt recovery. The phenolsulphonphthalein output at the time was 28 per cent the first half hour, 20 per cent the second half hour, 10 per cent the third, and 5 per cent the fourth, making a total excretion of 63 per cent. She was discharged from the hos-

pital in good condition on January 27, 1945. A recent communication indicated that the patient was entirely comfortable.

In conclusion, medical treatment has very little to offer these patients except general supervision and advice as to mode of living and diet. The progress in all cases is constantly, even if many times very gradually, down hill. It seems to me that more consideration should be given to the probability of surgical relief in many of these patients.

Medical Arts Bldg., Richmond, Va.

CHEMICAL STUDIES IN HYPERPARATHYROIDISM AND UROLITHIASIS

CECILIA RIEGEL, Ph.D., H. P. ROYSTER, M.D., G. J. GISLASON, M.D., AND P. B. HUGHES, M.D.

From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania, and the Departments of Urology and Surgery, Hospital of the University of Pennsylvania, Philadelphia

The increased frequency with which hyperparathyroidism is being found to be one of the etiologic factors in urolithiasis has supported the original observations of Albright, Baird, Cope and Bloomberg[1] and has led to more careful study of patients with bilateral or recurrent renal calculi. Although the characteristic blood findings of hypercalcemia, hypophosphatemia and hyperphosphatasemia may be sufficient for diagnosis in the usual case, the values for these substances may in some instances of hyperparathyroidism deviate only slightly from the normal. In such circumstances the determination of the increased urinary calcium excretion characteristic of this disease frequently provides the necessary additional information.[3] The importance of this latter finding cannot be denied, but we believe, in the light of recent studies made by us, that the finding of hypercalcinuria must be carefully evaluated before too great dependence is placed upon its diagnostic value.

In the routine study of patients with renal lithiasis in the urologic clinic, blood calcium, phosphorus and phosphatase studies are performed. In the past few months the program of study has been enlarged to include determinations of the urinary excretion of calcium and phosphorus in cases of recurrent bilateral or unilateral stones. This plan of study is conducted according to the method of Bauer and Aub,[4] in which the patient is placed upon a low calcium diet and the urine collected over a three-day metabolic period. The diet used in this hospital was neutral and contained approximately 2,200 calories and not over 0.1 gm. of calcium per day. In a series of normal individuals the urinary excretion of calcium was found to be less than 200 mg. for the three-day period and the phosphorus excretion to be approximately 1.9 gm. for the same period.

In a study of fifteen patients with urolithiasis, fourteen (93 per cent) were shown to have a definite increase in the renal excretion of calcium. The values obtained in the entire group ranged from 291 to 916 mg. per three-day period with an average of 469 mg. These figures are significantly elevated above the normal, and the degree of elevation approximates that found in a series of patients with proved hyperparathyroidism complicated by renal stone operated upon in this hospital (Fig. 1).

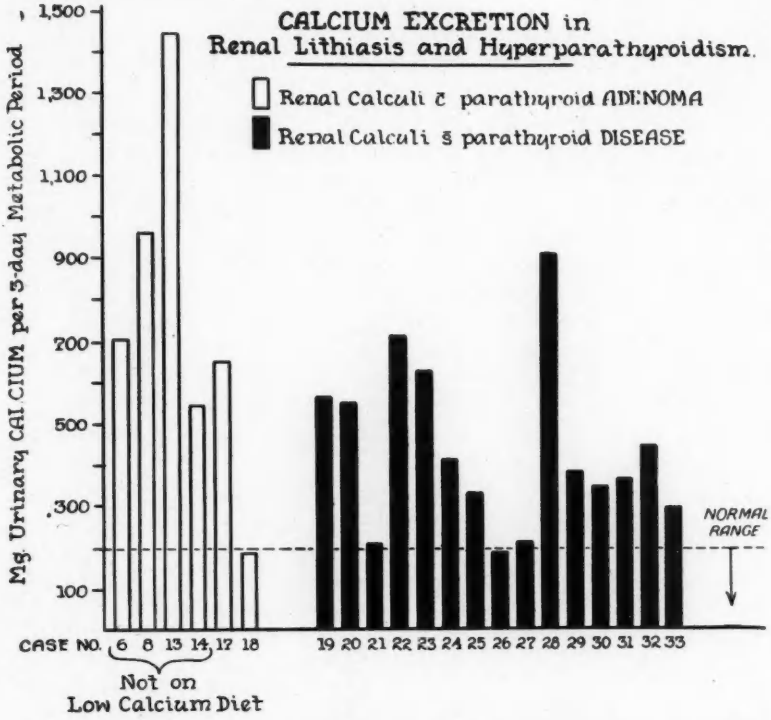

Fig. 1. Excessive urinary calcium excretion in patients with renal calculi as compared to a similar group with proved parathyroid adenomas.

The average blood calcium levels were normal except in one instance where it was 11.9 mg. per 100 c.c. and was noted in association with hyperproteinemia of 8.1 gm. per 100 c.c. The

serum phosphorus values ranged from 1.8 to 4.2 mg. although no patient exhibited consistently low figures. The only elevated blood phosphatase level was in the hyperproteinemic patient who had sarcoid disease involving the liver. The urinary phosphorus determinations were all within normal limits.

On the basis of material available from the literature, one would be justified in making a tentative diagnosis of hyperparathyroidism in these patients. Upon clinical examination symptoms referable to hyperparathyroidism were meager after exclusion of the complications of renal lithiasis. Further evidence to exclude hyperparathyroidism may be noted in the urinary phosphorus excretion. Since all values were within the normal range and since there was no phosphorus retention as noted by the normal blood levels, there existed strong confirmation that hyperparathyroidism was not present in this group of individuals. The only roentgen evidence of bone changes was in one patient with several bone cysts of the pelvis and femora. The normal blood studies, including phosphatase, lack of bone demineralization and failure to find an adenoma after extensive neck dissection, served to eliminate the diagnosis of hyperparathyroidism in this case.

Other causes of hypercalcinuria in this group of patients could be excluded: osteoporosis, hyperthyroidism, metastatic carcinoma of bone, Cushing's syndrome, et cetera. With the exception of the patient with sarcoidosis all were apparently normal, healthy individuals except for their renal stones. Blood chemical studies in four patients failed to reveal evidence of acidosis, and there was no reason to suspect this condition in the remainder.

In our group of patients all have had episodes of urinary tract infection subsequent to stone formation. Therefore, it is reasonable to assume that some damage has been done to the affected kidneys. In eight of these patients it was possible to demonstrate impaired renal function at or near the time of the calcium excretion study. The tests used were concentration and dilution, phenolsulphonthalein excretion, urea clearance, appearance time of diodrast on urographic examination, and blood urea nitrogen level. All tests were not performed on every patient, but enough information was obtained on each to indicate the functional state of the kidney. In only one was there nitrogen retention and that was of mild degree.

TABLE I. CORRELATION OF URINARY CALCIUM EXCRETION AND RENAL FUNCTION IN UROLITHIASIS

Calcium Excretion Impaired	*Renal Function Studies*
High	
14 Cases	7 (50%)
Low	
1 Case	1

Of the fourteen cases with hypercalcinuria, seven (50 per cent) were found to have impaired kidney function while in the remaining seven the renal function studies were normal (Table I). In the patient with normal calcium figures, the renal function was found to be impaired. These figures demonstrate that moderately damaged kidneys may not only excrete calcium, but that abnormally large amounts may be found in the urine.

DISCUSSION

The relation between renal function and calcium excretion has received little attention. Albright, Baird, Cope, and Bloomberg[1] reported on patients whose kidneys were so badly damaged that even in the presence of large parathyroid adenomas very little calcium was excreted. It has generally been assumed, therefore, that patients with "renal damage" or renal insufficiency with nitrogen and phosphorus retention would excrete small amounts of calcium. The above evidence seems to have been the basis for the assumption that the renal excretion of calcium is also depressed with less severe degrees of renal damage. On the other hand, our cases demonstrate that abnormally large amounts of calcium may be excreted by moderately diseased kidneys in patients otherwise normal and who do not exhibit azotemia. A search of the literature revealed that similar cases have been reported.[2,3,5,6] In a case of hypercalcinuria due to osteoporosis, Albright, Burnett, Cope and Parson[2] reported excessive urinary calcium excretion in the presence of kidneys with greatly reduced ability to concentrate albeit with normal phenolsulphonthalein excretion. In another report Albright, Sulkowitch, and Bloomberg[3] found excessive amounts of calcium in the urine following successful removal of a parathyroid tumor. Renal stones and infection persisted in the kidney, but no functional studies were mentioned. In a third case of renal stone with hypercalcinuria the neck and mediastinum were explored in

two stages without success. The further relation of renal function to calcium excretion was not investigated in any of these patients.

CONCLUSIONS AND SUMMARY

Hypercalcinuria was demonstrated in fourteen (93 per cent) of fifteen patients with renal lithiasis in whom hyperparathyroidism was excluded.

Fifty per cent of these cases exhibited evidence of renal damage.

This study demonstrates that moderately diseased kidneys may excrete excessive amounts of calcium in the urine in the absence of other demonstrable causes.

Hypercalcinuria in the presence of renal stone may not be a reliable diagnostic sign of hyperparathyroidism.

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FURTHER OBSERVATIONS ON NEPHROSTOMY

GEORGE R. LIVERMORE, M.D.

Memphis, Tennessee

In 1933 I presented a paper on nephrostomy before this Association. At that time I brought its value to your attention and reported four cases in which it had proved a life saver in my hands.

One of those cases, Mrs. C. D. O., is living and well today, having worn a nephrostomy tube in her left and only remaining kidney for more than nineteen years. The nephrostomy was done for anuria of sixty hours' duration, which an indwelling catheter, alkalies, stimulation, forced fluids and hot packs failed to relieve. Her tube is changed about every two months. She leads a normal life, does all her house work, has cared for an invalid mother and during World War II worked as a teller in a bank.

Since that time I have done this operation repeatedly and in most cases with very gratifying results.

At the 1937 meeting of the American Medical Association, I reported a case of anuria due to cresol poisoning in which bilateral nephrostomy and decapsulation were done with prompt establishment of diuresis and complete recovery. This man is alive and in perfect health today. That I am not alone in my appreciation of this operative procedure is evidenced by papers on the same subject by Boyd, Cabot and Holland, Graves and Buddington, Herman, Kimbrough, Rolnick, and Crane. The late Dr. H. L. Sanford reported three successful cases of nephrostomy and decapsulation for bichloride of mercury poisoning before this Association in 1936.

I have no new technique to offer, but have used that of Cabot in which a sound is passed through an incision in the pelvis to the lower calyx and the cortex incised over the tip of the sound. (Graves and Buddington use a malleable stylet instead of a sound. Herman has devised a nephrostomy cannula which has certain advantages.) A Foley bag catheter, 18 F., or the McIver tube, is then inserted through the nephrotomy wound into the pelvis, the bag inflated, a fat transplant sutured in the kidney with 00 catgut

sutures above and below the tube to control bleeding and close the wound.

If the kidney cannot be freed and the pelvis exposed, I do not hesitate to incise the cortex over the lower pole, insert my finger to make sure that the pelvis has been entered, put in the Foley bag catheter and proceed as in the previous technique.

Decapsulation is done in addition to nephrostomy in anuric cases and those in which we hope to improve kidney function, e.g., chronic nephritis. It is a mistake to wait too long before doing a nephrostomy as the kidneys may become so severely damaged (as evidenced by the autopsy specimens of Case 1, herewith reported) that they will be unable to excrete urine. Therefore, I urge that nephrostomy be done within the first forty-eight hours if other measures have given little or no results.

The value of nephrostomy in preventing the re-formation of stones in pelvic and calyceal stones in infected kidneys is too well known for further comment. Its value, too, in promoting passage of stones impacted in the ureter was reported by Keyes at the meeting of the American Association of Genito-Urinary Surgeons in 1943 and further confirmed by the author at the same time.

Indications for nephrostomy as noted by Lowsley and Kirwin are:

1. Failing renal function due to stricture, occlusion, or obstruction of both ureters or a soltary kidney as in calculus anuria, tuberculosis and malignant disease.

2. Anuria from acute nephritis of mercurial poisoning. (I would add phenols and arsenic.)

3. Dynamic disturbances of the renal pelves, ureters and bladder, preventing evacuation of the urine.

4. Bilateral renal calculi with severely damaged kidneys.

5. As a temporary measure to improve function in hydronephrosis or infected hydronephrosis in which the cause of obstruction is removable.

In the cases herewith reported, nephrostomy was done for the following reasons:

1. Reflex anuria following cystoscopy.

2. Intractable pain in the left and only kidney. Hydronephrosis, atonic, dilated and markedly trabeculated bladder.

3. Inoperable carcinoma of the bladder blocking right ureteral orifice of only kidney. Renal colic, frequency, burning and nocturia.

4. Staghorn recurrent calculus, left and only kidney, colic, rigors, fever and sweats.

CASE REPORTS

Case 1.—L., a white man, married, aged fifty-six, on November 10, 1945, had a stroke with partial paralysis, left side, which lasted two days. He underwent resection of the prostate on January 17, 1946, at which time the blood pressure was 196/130. The heart was normal.

He made a nice recovery and returned to work four weeks after operation. He was seen again on March 28, 1946. He complained of pain in the left loin. The blood pressure was 218/136. Urinalysis showed 2 plus pus and a trace of albumin. A No. 6 catheter was passed to right renal pelvis, from which there was a good flow of clear urine. The left orifice was stenosed and nothing could be made to pass beyond it. Indigo carmine appeared in three and three-quarter minutes from the right side and was deep in five minutes. It appeared in five minutes from the left orifice, but was very pale and only a trickle which never concentrated in fifteen minutes. Twenty-four hours later his wife reported that he had not passed any urine following cystoscopy. He was sent to the hospital and cystoscopy was repeated. A No. 5 catheter was passed to the right pelvis and 35 c.c. dark, blood-stained urine was aspirated. Nothing could be passed on the left side. He was returned to his room with the catheter in the right kidney draining nicely. In the following twelve hours, 300 c.c. urine drained from the catheter from the right kidney, but none was voided from the bladder. The next morning the nurse reported that the catheter had ceased draining repeatedly and that she had spent the night irrigating it with saline. The output of urine was not more than 30 c.c.

Left nephrostomy was advised and was done at 3 P.M., the catheter having been repeatedly irrigated but no urine output obtained. When exposed and freed, the kidney was found congested, swollen and edematous. An 18 F. Foley bag catheter was inserted through a nephrostomy wound into the pelvis without the use of the sound. No urine was found in the kidney pelvis and no urine drained from the nephrostomy tube from the time of operation until his death, but 510 c.c. drained into the bladder from the right kidney. He died at 8 P.M., seventeen hours after nephrostomy.

Autopsy showed hemorrhagic areas and multiple small abscesses throughout the parenchyma of both kidneys (Fig. 1), the spleen and the liver.

Comment: Had nephrostomy been done sooner, before the kidneys had developed multiple abscesses, excretion of urine from the left kidney might have been established.

Case 2.—Mrs. C. was a white woman, aged seventy-four. The diagnosis was stricture of the urethra; left infected hydronephrosis and dilated left ureter; atony of the bladder (Fig. 2). The bladder was so thickened and trabeculated that it had the appearance of one resulting from hypertrophy of the prostate of long standing. The patient had suffered for forty years with stricture of the urethra. She had had repeated, and in later years almost constant, attacks of frequency,

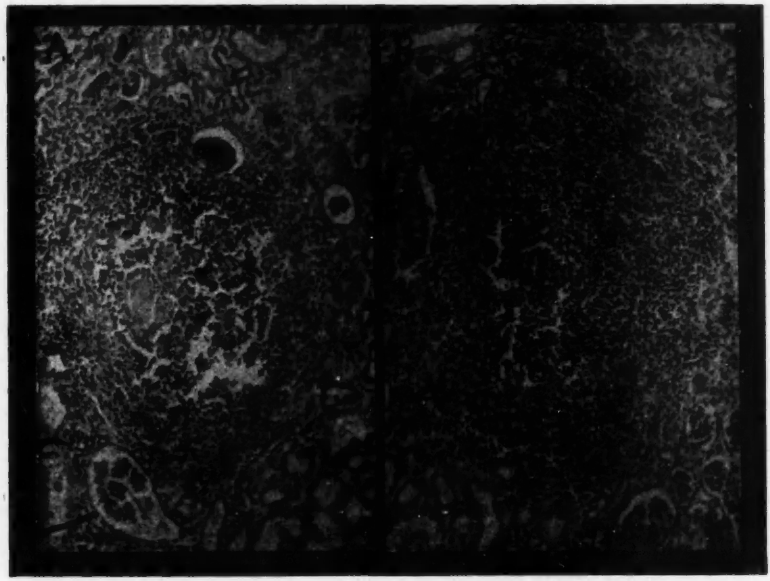

Fig. 1

nocturia, tenesmus, pain in the left loin and back and finally complete inability to void at all.

She underwent a right nephrectomy for calculous pyonephrosis in 1930. Dilations of the urethral stricture, left pelvic lavage, and an indwelling catheter were of only slight benefit, so finally a suprapubic cystostomy was done in the hope of improving the musculature of her bladder. This controlled the infection and made her comfortable, but when the suprapubic wound healed, her symptoms were the same as when I first saw her. Therefore, nephrostomy was done on her one remaining kidney and the ureter tied off to prevent any urine from entering the bladder.

She had a somewhat stormy convalescence, but survived even an attack of pneumonia and is now, one year after operation, in good health. She suffers at times with pain in her bladder, but irrigations of silver nitrate, 1 to 5000, followed with protargol 1 per cent and alypin 1 per cent, equal parts, left in the bladder, make her comfortable.

Case 3.—E. Y., a white man, married, aged forty-eight, was well developed and well nourished. The diagnosis was inoperable carcinoma of the bladder with occlusion of the orifice of both ureters. A

Fig. 2

catheter could be passed to the left kidney, but the orifice of the right could not be found. Therefore, nephrostomy was done on the left kidney, December 7, 1945, and free drainage of urine was established at once through the nephrostomy tube. He continued to have rigors, fever and sweats. The white cell count rose to 20,000. After several unsuccessful attempts to locate the right orifice, we made a diagnosis of right pyonephrosis. On December 22, 1945, a pyonephrotic right kidney was removed. He improved rapidly and left the hospital on January 1, 1946, in fair condition and free of pain. The nephrostomy worked perfectly. Report on the tissue from the bladder showed infiltrating carcinoma grade III.

Case 4.—S. W. B., a white man, married, aged forty-six, underwent a right nephrectomy for calculous pyonephrosis two years ago. One year later a staghorn stone was removed from the left kidney. He had had pain rigors, fever and sweats for two months before admission. An x-ray showed a large staghorn calculus in the left kidney. The stone was removed June 20, 1944, and a nephrostomy tube left in the pelvis of the kidney. The tube was removed on August 28, 1944, but all urine continued to pass from the nephrostomy fistula.

On September 10, 1945, at operation, the left ureter was found completely occluded by an impassable stricture at the ureteropelvic junction. The ureter was severed just below the stricture. The pelvis was incised, a McIver nephrostomy tube inserted and the severed ureter brought to within one-half inch of the kidney pelvis, to which it was sutured with long interrupted 000 chromic gut. Five days later, the nurse, by mistake, removed the nephrostomy tube. The next day the patient was anesthetized and a catheter was passed up the ureter. It was grasped with forceps through the nephrostomy wound and the tip pulled out so that the catheter part of the McIver tube could be tied to it. By pulling the ureteral catheter out through the urethra, the catheter of the McIver tube was drawn down the ureter. This was left in three weeks and when removed the larger portion of urine came through the nephrostomy wound. Repeated attempts were made to pass a catheter up the ureter to the kidney pelvis but without success.

He reported several months later. The nephrostomy tube had been removed two months and the urine was discharging through the fistula in the loin. An x-ray showed a large stone filling the pelvis and calyces. The fistula was dilated and an 18 F. catheter was passed to the pelvis and held in by adhesive strips through a safety pin in the tube. The phthalein output was so poor and the blood chemistry so high that further operative procedures were considered unwise. The Mayo Clinic concurred in this. This man, however, has been back at work in the past few weeks.

Medical Arts Bldg., Memphis, Tenn.

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DISCUSSION

DR. J. DELLINGER BARNEY (Boston, Mass.): I was very much interested in the paper by Dr. Senger on bilateral hypernephroma. Dr. Deming is connected with the case, I would like to mention, for he did a nephrectomy on the patient during the man's early middle life. Dr. Deming will know just what was done; the operation was for a carcinoma. The patient came eventually to our hospital, and there was evidence of a tumor of his thyroid and also a tumor of his remaining kidney. The thyroid was not suspected to be a malignant type, but was operated upon, and it proved to be of the same nature as the tumor of the kidney which Dr. Deming had removed.

We thought we should investigate the remaining kidney, so I exposed the kidney, found an obvious neoplasm and took a biopsy. The biopsy showed, I think, the same type of tumor that was found when Dr. Deming operated upon the other kidney.

If I had realized that these cases were so very uncommon, I should long ago have reported it. The man, incidentally, is living. He was superintendent or janitor in a hospital in Connecticut. Although the hospital won't let him go back to work, he is anxious to do so because he feels so well, in spite of all his troubles.

I want to congratulate Dr. Royster and his coworkers on their studies on hyperparathyroidism. I have been interested in the subject with Dr. Albright for a long time. I am just an innocent bystander, but I see the work and hear what is going on. We have had a great deal of trouble in determining that certain cases which eventually prove to be due to hyperparathyroidism are actually due to that condition because the phosphorus and calcium show nothing, and the bony changes are not demonstrated by x-ray. However, by estimating the total calcium in the urine, we were able to say that those cases were due to hyperparathyroidism, and were able to prove it by operation.

But the point I want to make, which I think is important, is that this disease and the study of hypercalcinuria ought not to go, as I think has happened, into the discard. There have been a lot of cases of hyperparathyroid disease that have not been found. It is a very important etiological factor in the formation of stone.

Just because phosphorus and calcium tests show nothing, we have a tendency to toss the condition aside as being not due to hyperparathyroidism, and then take out the stone and think we have done a grand job.

DR. REED M. NESBIT (Ann Arbor, Mich.): I want to discuss Dr. Livermore's paper. In mentioning the technique of nephrostomy, Dr. Livermore quoted Dr. Cabot and his technique. Then Dr. Livermore mentioned the fact in his own technique he introduces a nephrostomy tube, and following the introducing of the nephrostomy tube, he uses two sutures of 00 catgut with some fat in closing the kidney opening around the tube.

I think that I should emphasize the fact that one of the essential principles of the Cabot technique of nephrostomy is that the nephrostomy tube should be introduced by way of the kidney pelvis, and that the opening through the cortex of the kidney should be smaller than the tube that is introduced.

If one pulls through the cortex, beginning at the pelvis, a tube that is larger than the hole that has been created, then no sutures are necessary and no bleeding occurs.

DR. CLYDE L. DEMING (New Haven, Conn.): To clarify the case which Dr. Barney made reference to, I might say that that patient was a man about forty-five years of age who had a hypernephroid carcinoma of his kidney. Ten years later he developed his thyroid lesion, and shortly after that the lesion in his remaining kidney. Recently we have had an opportunity to follow our tumors of the kidneys, of which there are more than eighty, all of which have been followed. About twenty of those cases are available for microscopic study of metastatic lesions, and the frequency at which metastatic lesions occur in all of these renal malignancies is as follows: the lungs first, lymph nodes second, bones third, and the opposite kidney fourth.

DR. LEON HERMAN (Philadelphia, Pa.): In connection with Dr. Senger's presentation, I would like to record an unusual type of metastasis from renal hypernephroma. The patient, a woman, was admitted to the Pennsylvania Hospital with symptoms suggestive of bronchial carcinoma. There was a pedunculated neoplasm of the bronchus which biopsy study proved to be an adenocarcinoma. Some weeks after pneumonectomy, gross hematuria

appeared and examination disclosed a neoplasm of the kidney which proved to be identical in structure with the growth in the bronchus. In a second case, a bronchial sarcoma was found to be secondary to uterine sarcoma. Such experiences would suggest the desirability of investigating the kidney and other organs for primary new growth in certain cases of tumor of the bronchi. Incidentally, I think that the Kimball instruments are superior to all others in performing nephrostomy for simple drainage.

DR. D. M. DAVIS (Philadelphia, Pa.): I would like to mention one point which keeps recurring to me in connection with hyperparathyroidism. It is perhaps seldom considered that a majority of people with definite hyperparathyroidism and hypercalcinuria do not develop stones in the kidney or ureter. Why is this? This seems to me a more important thing to think about than the development of stones in the pelvis and ureter. There must be a reason. Might we not assume that other elements tending to cause stones to form and be retained are perhaps present in those patients with hyperparathyroidism who do develop stones in the kidney, pelvis and ureters, and that of these, of course, perhaps the most important is obstruction at some point? Therefore, we must not think that the presence of hyperparathyroidism rules out obstructive lesions in the urinary tract. We must think of them in our treatment, and it may indeed well be that in cases where, even after hyperparathyroid operation, hypercalcinuria persists, we can aid the patient to avoid the formation of further stones, even if he continues to put out excessive amounts of calcium, by not only removing the stones already present, but by taking great care to relieve any obstruction which may be present.

DR. JOHN A. TAYLOR (New York, N. Y.): Dr. Senger's paper brings up the question of multiple renal tumors. I, just briefly, would like to mention the case that I saw at the Hospital for Special Surgery. The patient was brought in, in extremis, with paraplegia due to metastatic lesions in the spine. The ribs were also filled with metastatic lesions. Genito-urinary consultation was asked to rule out carcinoma of the prostate. The prostate was normal. Biopsy of the rib showed hypernephroma. The patient died, and autopsy showed a bilateral benign adenoma of the kid-

ney plus a hypernephroma in the left kidney which had metastasized to practically every organ in the body.

DR. WILLIAM F. BRAASCH (Rochester, Minn.): With the aid of urography and other clinical data, more cases of polycystic kidney are being recognized these days. It is surprising how long some of these patients will live without much of any treatment; and in the long run, conservative treatment is the best procedure. The temptation to try some form of surgical treatment is very great in some of these cases, and every now and then a complication is found which is best treated by surgical means, as Dr. Dodson has shown. Twelve years ago Walters and I reported a series of eighty-five cases of polycystic kidney which were operated on at the Mayo Clinic for various surgical lesions.

Since most of the symptoms accompanying polycystic disease are secondary to renal insufficiency, the majority of patients will present themselves to the internist. However, with the onset of pain, hematuria, tumor or secondary renal infection, the urologist is usually consulted for relief.

Pain referred to one or both kidneys is not an uncommon symptom. As a rule it is an intermittent dull ache. When the kidneys are much enlarged, with evident ptosis, corsets have been adjusted with relief in some cases. Occasionally renal pain is quite severe and, in the absence of renal lithiasis or ureteral obstruction, retention of fluid in a distended cyst may be the cause. If there has been recent hematuria, a single large cyst may be distended with bloody fluid. Surgical drainage of these distended cysts may be followed by relief from pain. Surgical drainage of cysts for the usual dull renal pain will not give relief and is not justified.

The surgeon also may be tempted to try the so-called Rovsing's operation for drainage of the many cysts which are found on exposing the kidney. This was suggested first by Rovsing some fifty years ago, in hopes that the renal function would improve following relief of pressure caused by the cysts. This operation is often followed by disappointing results. In some cases the kidney tissue drains a long time after puncturing the cysts, and secondary infection may ensue. I remember one case particularly in which the Rovsing operation was done and infection followed, in spite of every precaution, and nephrectomy had to be done. In a recent review of our cases so operated, it was found that most of them

did not do very well. The average patient when left alone did much better. Very little improvement in renal function on that side followed drainage of the cysts. Some patients died within a year or two afterward, who probably would have lived longer without operation.

Over the years, members of this Association have reported cases from time to time in which the Rovsing operation was performed. As far as I know, but few cases were followed through and found to be greatly improved by the operation. However, when complications occur in the polycystic kidney such as stone, diffuse infection, and so forth, operation as reported by Dr. Dodson may be definitely indicated.

DR. ALEXANDER R. STEVENS (New York, N. Y.): I would like to ask if anybody has had any reason to operate on polycystic kidneys because of long hematuria. I have seen one individual who had bleeding off and on. I thought perhaps I should operate. Fortunately, the patient declined. However, the blood count remained good, there wasn't enough loss of blood to influence that. She ultimately came to operation because of infection.

One patient whom I reported two years ago, where the operation was done three years ago, is still living, leading a pretty active life, but has again had a recurrence of bleeding for a matter of months. If anybody has anything to offer on that, I would like to hear it.

DR. LEON HERMAN (Philadelphia, Pa.): As an addition to Dr. Dodson's paper I would like to describe a case of anuria complicating congenital single polycystic kidney. At the age of sixty-five, this patient, a woman, was admitted with gross hematuria which came from the right kidney, the left one being congenitally absent. Urographic deformities of the pelvis led to the tentative diagnosis of renal neoplasm. Several years later she suffered severe renal colic followed by anuria, and was admitted two days later with advanced uremic symptoms. Responding rapidly to ureteral catheter drainage, stereoscopic ureteropyelograms disclosed displacement far forward of the proximal portion of the ureter which in passing over a large tumor or cyst has become occluded. Exploration disclosed four cystes the size of English walnuts in the exposed portion of the kidney, and a cyst about the size of a

small grapefruit springing from the inner portion of the lower pole of the kidney with forward displacement of the ureter. The cyst was filled with blood clot. Intracystic hemorrhage explained both the pain and subsequent anuria. Owing to the seriousness of the situation, we merely opened the cyst, partially evacuated its contents and inserted a large drain. The patient, now seventy-three years of age, is quite well.

As regards the control of serious hemorrhage from polycystic kidney by operation, we have seen only one case in which massive hemorrhage from the left kidney threatened life. In the case of this patient, a young man, the Rovsing procedure was followed and the bleeding ceased. The patient died about five years later as the result of uremia without recurrence of the bleeding.

We have a polycystic case in the person of a dentist aged sixty-five, who has been bleeding off and on, and at times massively, for a period of eight years. Six months ago his bladder filled with clots which had to be evacuated mechanically. Despite this episode and the fact that he has brief periods of serious bleeding at infrequent intervals, I would not favor operative treatment.

Dr. George F. Cahill (New York, N. Y.): About five years ago Dr. Fish and I read a paper on a series of operations upon polycystic kidneys in which, from our experience, we laid down the operative indications in polycystic disease. First, cases with polycystic disease may suffer from any other urologic pathologic condition similar to normal individuals: infection, stone, tumor or even nephritis may occur in these. They should be treated for their pathologic lesion without or with consideration of their polycystic kidneys, depending upon circumstances. Secondly, these cases suffer from the effects of polycystic disease. In these, hemorrhage, infection, obstruction or anuria may occur. Hemorrhage is frequent and may require operative intervention. We showed its value in one particular case, in which subsequently, due to the relief from the effects of the decompression of the cysts, the patient went on in a normal life, having several children without difficulty.

Dr. Fedor L. Senger (Brooklyn, N. Y.): I just want to thank the gentlemen for their discussion.

In regard to Dr. Deming's remarks, we know that the tumors metastasize to the kidney, but some of those reported in the literature seem to be primary tumors.

Dr. Barney's case is extremely interesting in that he has a thyroid metastasis. In the article that I mentioned that Dr. Lubaarsch published, he alleges to have seen eight patients with thyroid metastases, all of whom, however, had a pre-existing adenoma.

DR. AUSTIN I. DODSON (Richmond, Va.): I wish to thank the gentlemen for their discussion. I, of course, did not mean to imply that every patient with polycystic disease should be operated upon, but certainly when they have pain or when there is evidence of infection. Considerable benefit can often be obtained by draining the cysts and improving drainage from the renal pelvis. I noticed in two patients that I operated upon that renal obstruction seemed to be caused by a cyst pressing upon the renal pelvis. There was dilatation of the renal pelvis in addition to the usual deformity. In some instances such obstructive lesions are the cause of pain and no doubt play some part in the destruction of the kidney.

DR. BOLAND HUGHES (Philadelphia, Pa.): I would like to reemphasize one point, if I may, concerning the urinary calcium excretion in diseased kidneys. It concerns a patient on whom we did differential urinary calcium studies.

The slide will show that the kidney that had a more impaired function excreted the greater amount of calcium.

[Slide] This patient had two stones, one in the left and one in the right kidney. This is a proved case of parathyroid adenoma which was removed surgically. You can see that his blood calcium before the parathyroidectomy was 12, and his urinary excretion approached 700 in the three-day period.

At this point his parathyroid adenoma was removed; then one of the stones jumped from his right kidney into the right ureter, completely obstructing the right upper urinary tract, giving a kidney which on urogram showed no function, and it was necessary to do a right ureterolithotomy. A ureterostomy was done at this point, and we were able thereafter to do differential calcium studies, and we found that the right kidney that excreted only 5 per cent P.S.P. in fifteen minutes had almost 300 milligrams of calcium in three-day urine, in contradistinction to the kidney that was not very much functionally impaired, which had only 200. This did not apply, however, to phosphate excretion, because the kidney

that was better functioning did excrete more urinary phosphorus, so I merely wish to re-emphasize that diseased kidneys sometimes excrete more urinary calcium than normally functioning kidneys.

QUESTION: The concentration of P.S.P. was less from the kidney that was excreting the greater amount of calcium?

DR. HUGHES: Yes.

DR. GEORGE R. LIVERMORE (Memphis, Tenn.): I want to thank Dr. Nesbit for calling me down on reporting Cabot's operation. What I meant was I used the sound in the way Cabot does. I do a nephrotomy because I once saw a surgeon use the Cabot technique and leave a stone in the upper calyx. After that experience I have preferred nephrotomy and examination of the pelvis and calyces in order to prevent such a calamity.

TREATMENT OF STRESS INCONTINENCE IN WOMEN

JOHN K. ORMOND, M.D.

From the Division of Urology, Henry Ford Hospital, Detroit, Michigan

Incontinence of urine is probably the most discouraging non-malignant condition with which we have to deal, and may be divided into four classes: (1) fistulas, (2) psychogenic incontinence, (3) neurogenic incontinence, and (4) myogenic incontinence.

Fistulas need only to be mentioned. They present a special problem differing in nature from any of the others.

The commonest example of psychogenic incontinence is enuresis. We may be doing an injustice to some of our patients in classifying enuresis in this category. Many of the children, especially the girls, can be cured by treatment and most are relieved at puberty, but certainly the majority of those whose trouble persists after puberty show psychic abnormalities, whether the cause or the result of the condition being undetermined. They are a pitiable group concerning whom we have heard a great deal from the Army surgeons.

The other two classes—neurogenic and myogenic—depend on some tissue defect which may be congenital, developmental or traumatic in origin.

So far as achieving anything like a normal condition is concerned, the neurogenic type is the most hopeless, the myogenic type presenting a more hopeful problem. Congenital myogenic incontinence is exemplified by epispadias, and traumatic myogenic incontinence is seen following injuries and operations—notably parturition and transurethral surgery. The commonest form is stress incontinence in women, usually occuring in parous women past middle life and usually, though not always, dependent on injury during childbirth or during operative repair of defects the result of childbirth. A few instances are seen in nonparous elderly women due to rather obscure causes. This condition lies on the borderline between the fields of gynecology and urology. In some clinics all are handled by the gynecologists. In our clinic, all patients with complaints arising in the urinary organs are referred, at least for consultation, to the Division of Urology. This seems reasonable and to the patient's advantage; in the first place, the differentiation between

urgency and incontinence is sometimes not as simple as might be expected; and in the second place, only the minority of patients with stress incontinence require operation—the others being, if not completely relieved by attention to the posterior urethra and trigone, at least relieved to the extent that their condition is very tolerable, and is no longer more than a slight annoyance instead of an embarrassment. A careful history and cross examination are often necessary to determine whether there is in the individual instance, true stress incontinence or merely urgency. There may be both, but in true stress incontinence, without any conscious desire to void, on exertion such as lifting, stooping, laughing, coughing or sneezing, a varying amount of urine is expressed. In aggravated cases the clothes may be soaked, and in some even the slight exertion of walking causes this gush.

Examination consists of inspection and palpation of the urethra and perineum; catheterization to determine the bladder capacity, the absence or presence of residual urine, the calibre and course of the urethra, and for urine specimen; and a pelvic examination by an experienced gynecologist. All patients are given the benefit of one routine treatment consisting of dilating the urethra with Hegar dilators up to a No. 10 (30 F.) if possible, an irrigation of the bladder with boric solution and injection through the urethra into the bladder of 10 per cent argyrol in noninfected bladders, and of 1 per cent acid fuchsin where there is pyuria. When infection is present, a course of sulfadiazine is given; some few are benefited by this one treatment.

After this the course depends on the findings of the gynecologists. Where there is definite remediable abnormality—descensus, relaxed or torn perineum—rectocele, and especially cystocele—the patient is referred to the gynecologists for repair; and most of them are relieved of their urinary trouble by such operations because the gynecologists have learned to pay special attention to the urethra and bladder neck during the course of such procedures. Some few obtain no relief, or inadequate relief, and they are again referred to the Division of Urology—as are the few patients who acquire stress incontinence following gynecological operations.

Those patients who have no detectable abnormality of the pelvic floor or only very minor abnormality, and those referred back by the gynecologists, are given further treatment. The urethra is di-

lated once or twice a week——a meatotomy being done when necessary to permit the introduction of the large sounds; endoscopic and retrospective cytoscopies are done and the posterior urethra and trigone may be treated with 5 or 10 per cent silver nitrate at intervals of two weeks. On this regime many show marked improvement, enough so that their condition, if not completely relieved, amounts to only an annoyance and is easily cared for by a perineal pad. They do not need any operation.

It is said that some yield to hormone treatment, and I have seen at least one patient in whom I believed that there was an allergic basis for her symptoms.

The procedure outlined above leaves only a few patients whose symptoms continue as an embarrassment and prevent normal social life; and for their relief many operations have been devised. Some forty years ago Howard A. Kelly devised an operation for the relief of this condition and published it a few years later. He reported a high percentage of cures and stated: "The key to successful treatment lies at the internal orifice of the urethra and in the sphincter muscle which controls the canal at this point. I have succeeded in relieving every case where there had not been destruction of the tissues at the urethral orifice." Fulkerson in 1939 quoted Kelly and corroborates him from his own experience.

The operation as described by Kelly has been used in a great number of instances by a large number of surgeons, but without the great measure of success claimed by Kelly. Due to this, numerous other operations have been devised to remedy this condition.

Kelly's operation consisted of a plicating mattress suture inserted at the vesical neck, repairing and tightening the tissues at that point. It was, therefore, a reparative operation in contrast to most of the other operations devised which were nearly all substitution operations. A reparative operation attempts to repair the structures normally present, while a substitution operation attempts to substitute some other structure for the normal structure, usually a sling support of some kind. Of these substitution operations there are several.

Goebell transplanted the pyramidalis back of the symphysis, the ends being sutured under the urethra at its juncture with the bladder. The pyramidalis was left attached only to the pubis.

Frangenheim left the pyramidalis attached to the overlying fascia as well as to the pubes and combined strips of fascia with the muscle, as by Goebell.

Stoeckel combined the above procedures with a vaginal plastic and plication of the muscular structures about the vesical neck.

Giordano wrapped part of the gracilis muscle about the urethra. Deming has used this in the male, and others have reported success in the female.

Squier used the levator ani muscle beneath the urethra.

Thompson used strips of rectus and fascia brought down in front of the symphysis around the urethra. Norman Miller reported success with this method.

Martius mobilized the bulbocavernosus muscle and some fat and transplanted this mass between the urethra and the vaginal wall.

Price used strips of fascia lata, bringing them under the urethra and suturing them to the recti.

Aldridge used strips of the aponeurosis of the oblique muscles, bringing them through the recti, behind the pubis and around the urethra.

In addition to these, various operations have been described for twisting, angulating or stricturing the urethra, and recently Macky has described an operation on the trigone from within the bladder.

Many of these have been used in the treatment of stress incontinence, and reports of their use still appear in the literature. However, they are not generally successful and moreover are better adapted to the treatment of neurogenic incontinence than to myogenic incontinence. Their use in cases of stress incontinence is evidence that the simple Kelly operation is not universally successful and that something further is desirable; and it now seems probable that that "something further" has been attained.

Our knowledge of the anatomy and physiology of the urinary control mechanism in women has been vague. But approximately ten years ago William T. Kennedy of New York began a serious study of this, stimulated thereto by the bad results he had obtained in operating for stress incontinence. He studied the control mechanism by inserting into the urethra a rubber tube or bag filled with x-ray opaque liquid and making pictures at various stages of urination. His conclusions were that there is an involuntary sphincter muscle about each of the inner and outer thirds of the urethra;

and that there is an additional sphincter, probably under voluntary control, about the middle third of the urethra, and that this is more important than the other two. He also concluded that the causes of incontinence are (1) trauma to the inner and middle third sphincters of the urethra causing them to become partially fixed by fine bands to the posterior lateral margins of the pubic rami, and (2) damage in the midline to those voluntary fibers which pass under the middle third of the urethra and are attached to each pubic ramus posteriorly, constituting a sling support.

He further concluded that the conditions for cure of incontinence are (1) the breaking of the fine bands between the urethra and the posterior lateral portions of the rami, and plicating the urethra in the midline vaginally to prevent reformation of these connecting bands and (2) bringing together in the midline beneath the inner and middle thirds of the urethra the uninjured portion of the "sling" fibers which are attached to the posterior aspect of the ramus.

He later concluded that the voluntary sphincter is composed of anterior fibers of the levator muscles which unite in a median raphe beneath the midline of the urethra, apparently more along the middle third, but also along the inner third of the urethra. Also that an important factor in causing incontinence is the abnormal position of the bladder and urethra caused by relaxation or sagging into the vagina.

On the basis of these conclusions he devised an operation for the cure of this condition which he and others have used with great satisfaction. It consists in breaking all adhesive strands binding the urethra to the pubic rami, plicating the floor of the urethra and restoration of the normal support of the urethra where necessary. This operation is done in the following way: A mushroom catheter, or preferably a Foley catheter, is inserted into the urethra, and the bag inflated. This is to facilitate recognition of the bladder neck. The cervix is grasped with a tenaculum and the vaginal wall incised along the urethra from shortly behind the meatus to well beyond the bladder neck. Then by blunt dissection, using the handle of the knife or a Küttner dissector, and keeping close to the rami of the pubis, the urethra is dissected free from the ramus on each side. This dissection must be done gently, with strokes directed medially. It is necessary to keep close to the bone to avoid a plexus of veins

and branches of the inferior vesical artery, and the dissection must extend well about the bladder neck into the paravesical space. As it is done the breaking of the fine adhesions between the urethra and the rami can be felt, and freedom of motion of the urethra and internal sphincter is restored. In order to maintain this freedom of motion, the tissues under the urethra are plicated by three mattress sutures, the posterior suture being similar to the old Kelly stitch. Then another row of mattress sutures brings together over the first row of sutures the tissues on each side of the urethra, bringing together the edges of a fascia-like structure that lies there.

Any redundancy of the vaginal wall is then removed, and if there is no appreciable redundancy, a strip is cut from each vaginal flap in order to remove whatever damaged portions of the voluntary sphincter there may be. Then the remaining fibers of this muscle are brought together beneath the urethra by 3 chromic catgut sutures. These sutures are passed through the vaginal wall close to the rami to be sure to pick up the fibers of the voluntary sphincter. Silver wire may be used. A catheter is left in place for a few days. Kennedy warns that any factor such as infection or hematoma beneath the restored urethra may dissolve the plicating sutures and allow the urethra to resume to some extent its preoperative position, and may cause failure. He recommends free drainage of the paravesical spaces and open vaginal wall flaps to forestall this.

In our clinic in the urological division we treat only the patients with no relaxation, and as explained before, the majority of those we care for do not come to operation. Therefore, I have had occasion to use this operation only three times. The first was a failure: the patient was no worse, but she was no better. This may have been due to technical errors on my part or to the reasons of which Kennedy warns. The other two were brilliantly successful. In the past I had used Kelly's operation a half dozen times, only once with complete and unquestioned success. In 1943 Counseller reported on his results. He gave the Kelly and other operations credit for 60 to 75 per cent cures, but out of twenty-six Kennedy operations he had not had a single failure. It seems, both from the rational basis of this operation and from the results obtained, that this is the operation of choice for this condition.

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AMICROBIC PYURIA

FRANK C. HAMM, M.D.
Brooklyn, New York

Cases of so-called amicrobic pyuria constitute a small but important group of urinary infections. They differ from the usual type of pyogenic infections, in that no organisms can be demonstrated, either by culture or by a Gram stain of the urinary sediment and they do not respond readily or consistently to any of the known forms of therapy.

The absence of organisms and the resistance to treatment immediately suggests the possibility of urinary tuberculosis. This possibility was ruled out in the seven cases which form the basis of this report, by repeated stains for tubercle bacilli and by guinea-pig inoculations.

In 1933 Wilbolz addressed the French Congress of Urology on this subject. He credits Faltin with the first report in 1909. Several papers, chiefly by Scandinavian authors, then appeared. Runeberg reported thirty cases in which ten underwent nephrectomy; histologic examination of these kidneys revealed no evidence of tuberculosis, but in some cases staphylococci were seen imprisoned in the cortex. Peters (1922) reported fifteen cases, in which five had undergone nephrectomy. No evidence of tuberculosis was reported and no organisms were observed. Nephrectomy was not indicated in any of our cases and it seems an unlikely possibility, as recent observers agree that persistent treatment is rewarded with complete recovery. Very few papers appear in the English literature. Brigg reported three cases; Cook described his observations in twelve cases. The incidence must be very small, only seven cases were found among a very large number of urinary infections among service men in one of the large Army General Hospitals.† The condition has been reported as occurring occasionally in the female but it is predominantly a disease of the young adult male. Our cases were young men ranging from nineteen to thirty-two years of age.

†Wakeman General Hospital, Camp Atterbury, Indiana.

SYMPTOMS

The symptoms are severe, with sudden onset of dysuria and frequency up to every few minutes day and night with suprapubic pain and terminal hematuria. The onset in three of these cases was preceded by a nonspecific urethritis of from one to three weeks' duration before the onset of bladder symptoms. Chills were not present in any case; two had low-grade fever averaging 99° to 100° F. and only occasionally touching 101° F. Leukocyte counts were slightly

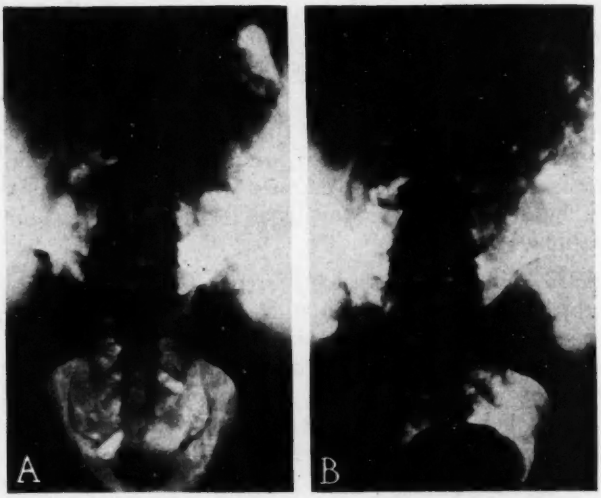

Fig. 1. Case 6. *(A)* Urogram shows markedly contracted bladder (capacity 50 c.c.) with irregular outline. Upper urinary tract findings not marked. *(B)* Urogram made after recovery, presenting normal sized bladder.

elevated (10,500 to 10,800), and the sedimentation rate was elevated in one case (No. 1) to 45 in one hour. Blood chemistry findings were in the upper limits of normal during the acute phases. The symptoms are so severe during the acute period, which may last several weeks, that the patient is confined to bed most of the time.

Physical examination was essentially normal, except in one thin young soldier in whom the contracted bladder could be palpated suprapubically as a firm, tender mass about 8 cm. in diameter.

The cystoscopic and pyelographic changes were more marked than that observed in the usual pyogenic infection. A picture of severe diffuse cystitis, with markedly contracted bladder, was the rule during the early acute phase (Figs. 1, *A* and 2, *B*). In two instances masses resembling neoplasm were found in the bladder (Fig. 3, *A* and *B*). Biopsy specimens were reported as inflammatory. The masses subsequently disappeared as healing progressed (Figs. 3, *C* and *D*).

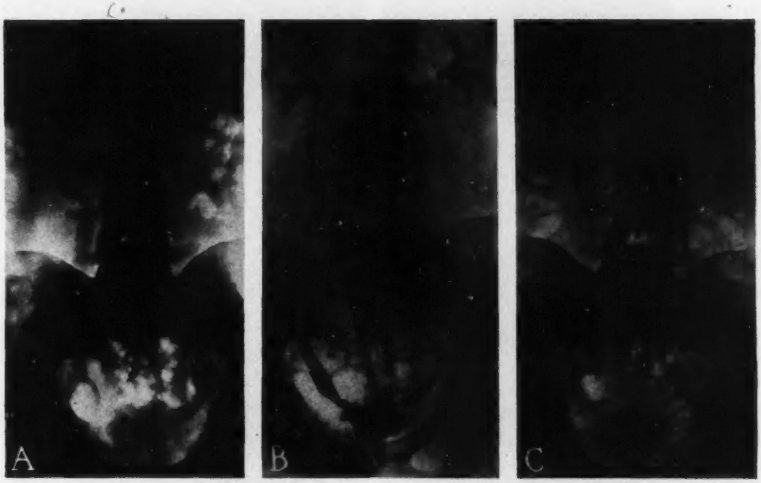

Fig. 2. Case 7. *(A)* Intravenous urogram made during acute phase shows marked dilatation of both pelves and calyces. *(B)* Urogram taken during early recovery shows markedly contracted bladder with irregular outline and dilatation of both lower ureters. Upper urinary tract is returning to normal. *(C)* Urogram taken after recovery shows normal outline of bladder. Upper urinary tract appears normal.

One of the constant findings was a generalized dilatation of the upper urinary tract. Figures 2, *A* and 3 *B* shows dilatation of the pelves, calyces and ureters in both kidneys. I am unable to state whether this dilatation is the result of the obstruction in the lower ureters from the contracted bladder, or whether the upper urinary tract is involved in the severe infection. The catheterized urine from the kidneys was free from pus in two instances, and in none of our cases was pus present in a marked degree from either kidney.

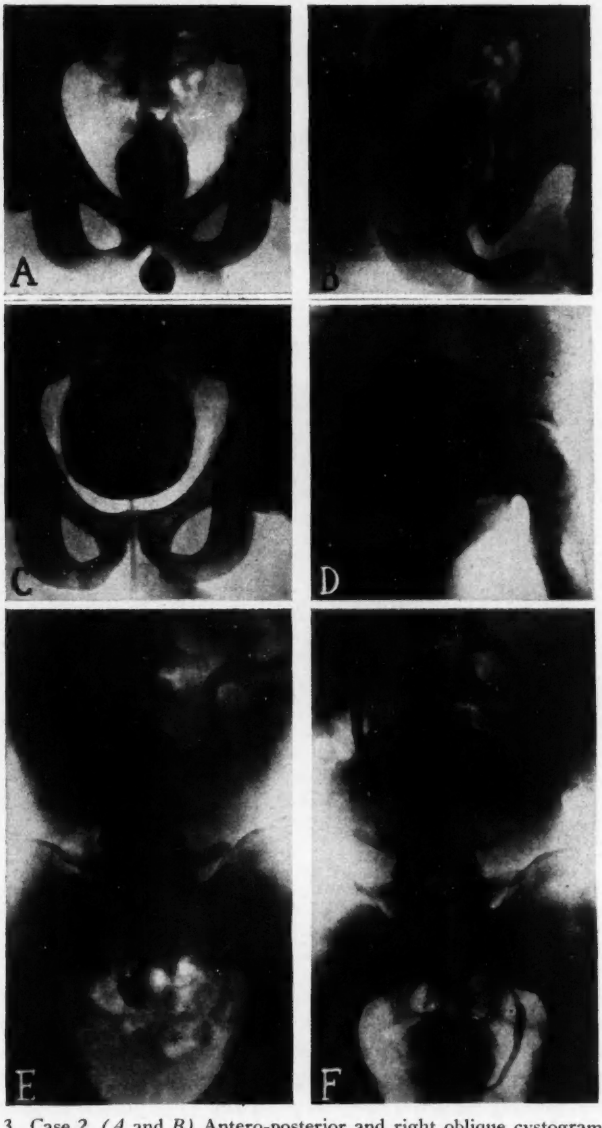

Fig. 3. Case 2. *(A* and *B)* Antero-posterior and right oblique cystograms taken during acute phase show generalized contracted bladder with marked filling defect in dome which resembled a neoplasm when viewed through cystoscope. *(C* and *D)* Antero-posterior and right oblique (45°) cystogram taken after recovery. *(E)* Ureterogram shows moderate dilatation of both pelves, calyces, and upper ureters. *(F)* Following recovery.

This observation does not agree with others and it is difficult to explain except that this is essentially an infection of the bladder. Ureteral catheterization is impossible in some of these markedly contracted bladders, so that specimens were not collected in every instance during the acute stage. In one instance, reflux up one ureter and contracted bladder were demonstrated during the acute phase. (Fig. 4). Upon recovery the function of the uretero-vesical valve was restored.

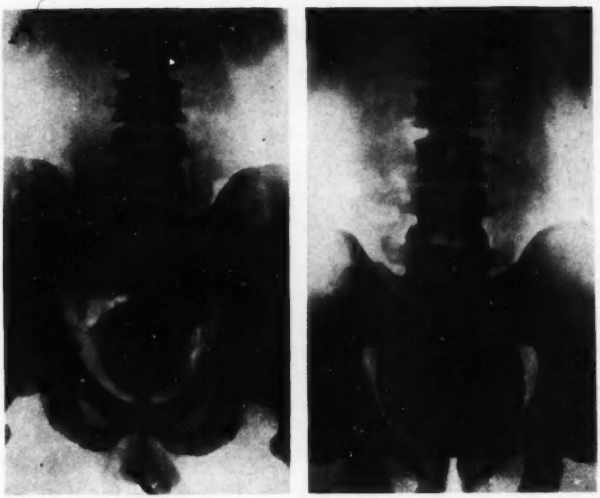

Fig. 4. Case 1. *(A)* Cystogram demonstrates contracted bladder with reflux up left ureter. *(B)* Cystogram made after recovery shows normal outline of bladder and no evidence of reflux.

TREATMENT

Arsenobenzine compounds have been recommended by European writers. Mapharsen was the only arsenical compound available at the time these cases were under observation. It was given in doses of 0.3 gm. every five days for five doses. Improvement was noted in each instance but cure cannot be attributed to this agent alone. Perhaps there is sufficient difference in the formula of this arsenical to make it less effectual than other members of the neosalversan group. A similar response was noted by Cook, who did not secure

final and complete recovery until foci of infection were removed. All of our cases were examined by Dental and Nose and Throat Sections for foci of infection, and no foci were reported. Sulfadiazine and sulfathiazole were of no benefit in our cases. They were given usually in courses of ½ to 1 gm. four times daily for five days. No improvement was noted following the administration of penicillin. Six of our cases received one or more courses consisting of 30,000 units every three hours for seven days, given intramuscularly.

Three cases received streptomycin. In general, the results obtained were satisfactory. It was given in doses of 160,000 units every three hours for seven days. Two patients apparently recovered after one course; the third was markedly improved after the first course, however the pyuria did not completely clear up until the second course had been given.

DISCUSSION

This condition is essentially resistant to all forms of therapy. The duration varied from two to nine months. It appears to be self-limited to a certain degree. The course is modified and the symptoms relieved by intramuscular administration of streptomycin and intravenous arsenicals (mapharsen), but in our experience neither of these agents can be considered as a specific cure. The use of arsenicals in the treatment of this infection has raised the question of syphilis as an etiologic factor. This possibility has been largely abandoned. Only one of the seven cases had a history of syphilis. Some observers favor the staphylococcus as the offending organism. It is true that this organism is occasionally found on culture even when no organisms can be seen in the stained sediment. The lack of prompt response to treatment, the absence of marked systemic reaction to such severe infection, suggests the possibility of a virus infection. Three of our cases started as a nonspecific urethritis. There may have been more, our attention was not attracted to this point in the history in our first cases. Some of these cases of nonspecific urethritis may have been caused by a virus. Cook suggests that the changes observed in the urinary tract are produced by toxins from organisms situated in a focus of infection. From observing the cases reported here, it is our belief that they are true infections of the urinary tract, possibly originating in the urethra,

ascending in character and probably caused by an ultra-microscopic organism as yet unidentified.

ABSTRACTS OF CASES

In each of the seven case histories which are briefly reported, the patients received one or more courses of sulfadiazine which was administered in doses of ½ to 1 gm. four times daily for five days. All received one or more courses of penicillin which was administered 30,000 units every three hours for seven days. In each case, studies were also made to exclude the possibility of tuberculous infection.

Case 1.—A white male aged twenty-four was first observed at a General Hospital overseas. His chief complaint was inability to void for eight hours; severe pain over the bladder area, severe dysuria, frequency and hematuria. Cystoscopy revealed the presence of a mass in the dome of the bladder whose appearance resembled that of a neoplasm. Specimens were obtained which were reported as inflammatory. Repeated cultures and stains were negative for bacteria. Mapharsen was given in doses of 0.3 gm. for five days for five doses, followed by moderate improvement in the signs and symptoms. The patient eventually recovered after a total period of eight months' hospitalization. Final check-up pyelograms and cystograms made following recovery revealed a normal urinary tract (Fig. 4).

Case 2.—A colored man aged twenty-five was observed during the entire course of his illness which lasted three months. On admission he complained of intense suprapubic pain with severe dysuria and frequency and hematuria. He also gave a history of untreated syphilis. A Wassermann test five months previously was positive. At cystoscopy a lesion was seen in the dome of the bladder. This resembled a neoplasm 1½ by 3 cm. but was found to be inflammatory tissue. During the course of the illness the patient was given a course of penicillin for twenty-two days in doses of 30,000 units every three hours. Following this, sulfadiazine, 1 gm. q.i.d., was given and this was followed by streptomycin, 160,000 units every three hours for ten days. A second course of streptomycin was given for three weeks in dosages of 120,000 units every three hours for seven days, and following this the patient recovered (Fig. 3).

Case 3.—A white man aged twenty-three was observed during the entire course of his illness which lasted two months. Treatment included five injections of 0.3 gm. mapharsen given at five-day intervals. He also received 120,000 units of streptomycin every three hours for a total of 7,680,000 units. He obtained a good result and was returned to duty.

Case 4.—A colored officer aged twenty-eight had specific urethritis of two weeks' duration before symptoms of dysuria, frequency and

hematuria appeared. The total duration of the infection persisted for four and one-half months. He received five injections of 0.3 gm. of mapharsen given at five-day intervals for five doses. A marked improvement was noted in this instance but pyuria persisted for several weeks. This finally cleared up and the officer was returned to duty.

Case 5.—A white man aged thirty-two was under observation during the entire course of his illness which lasted five months. The onset of his symptoms was not quite as severe as most of the other cases; however, dysuria, frequency and hematuria were the principal symptoms. His symptoms also differed from all of the other cases in that he had a low-grade fever for over two months. During this time his temperature went as high as 101 degrees. The patient also lost considerable weight. He received in conjunction with the above-mentioned treatment one course of streptomycin from which he apparently derived no benefit. He received mapharsen 0.3 gm. every fifth day for five doses with only slight improvement. Following this he received another course of streptomycin, 1,000,000 units daily for seven days, followed by complete recovery and return to duty. A persistent recurrent hematuria was an outstanding feature in this case.

Case 6.—A white man aged nineteen had a urethral discharge one month before admission to the hospital. Stains failed to reveal the presence of gonorrhea. Shortly before admission the patient experienced severe dysuria, frequency, nocturia, and hematuria. He was hospitalized five months. He did not receive streptomycin as it was not available. He appeared to be almost entirely well after two months of treatment when a relapse occurred and it was necessary to continue hospitalization for three months (Fig. 1).

Case 7.—A white male aged twenty-six had mild symptoms of dysuria, frequency, and a urethral discharge for two weeks before onset of severe symptoms of dysuria, frequency, nocturia and hematuria. Symptoms developed overseas. He reported to the hospital where he received penicillin and sulfanilamide. He passed a large amount of blood with clots in his urine. Upon evacuation to the U. S. the patient was voiding approximately every ten minutes day and night. Upon arriving at our hospital he received five injections of mapharsen, 0.3 gm. every five days with improvement but moderate pyuria persisted. The infection finally disappeared after five months' hospitalization. Streptomycin was not available at this time (Fig. 2).

80 Hanson Place, Brooklyn, N. Y.

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INCOMPLETE REDUPLICATION OF THE BLADDER WITH CONGENITAL SOLITARY KIDNEY

REPORT OF A CASE

EDGAR BURNS, M.D., HAROLD CUMMINS, PH.D., AND JACK HYMAN, M.D.

From the Departments of Surgery and Anatomy, Tulane University School of Medicine and the Department of Urology, Ochsner Clinic, New Orleans

The recorded cases of complete and incomplete reduplication of the urinary bladder, including division by bladder septa, are difficult to analyze because some of the earlier cases are vaguely described. Cathelin and Sempé, in their study of cases recorded up to 1903, pointed out that in some instances cases of vesical diverticulum had been erroneously reported as reduplication. Most of the early cases were discovered at autopsy. As diagnostic methods have improved, cases have been reported at more frequent intervals and an increasing number of these are being discovered in living persons. The variation in the pattern assumed by this anomaly has led to a confused and loose terminology; Wehrbein, for example, suggested that Michelson's case (Case 26) might be more correctly termed biocular rather than double bladder as reported. On the same basis, it might be questioned as to whether the case here reported should be designated as a bladder septum or reduplication. In denoting the location of the septa we believe that the terms "frontal" and "sagittal" give a more specific description of the anomaly than "longitudinal" and "transverse" as used in some of the recorded case reports.

The cases we have reviewed have been arranged into groups according to the pattern into which they seem to fit best (Figs. 1 to 6). Since cases in the same group differed somewhat, a brief abstract of each case will be given in order to clarify these differences.

GROUP I—COMPLETE REDUPLICATION OF THE BLADDER (FIG. 1)

1. (1871) Schatz described the case of a stillborn child with complete reduplication of the bladder associated with reduplication of the other pelvic organs. Two uteri opened into separate vaginas. Each

bladder was in communication with one vagina. There was a persistent cloaca, into which the vaginas and rectum opened.

2. (1878) Smith reported a case of complete reduplication of the bladder with double penis so that each bladder communicated with a

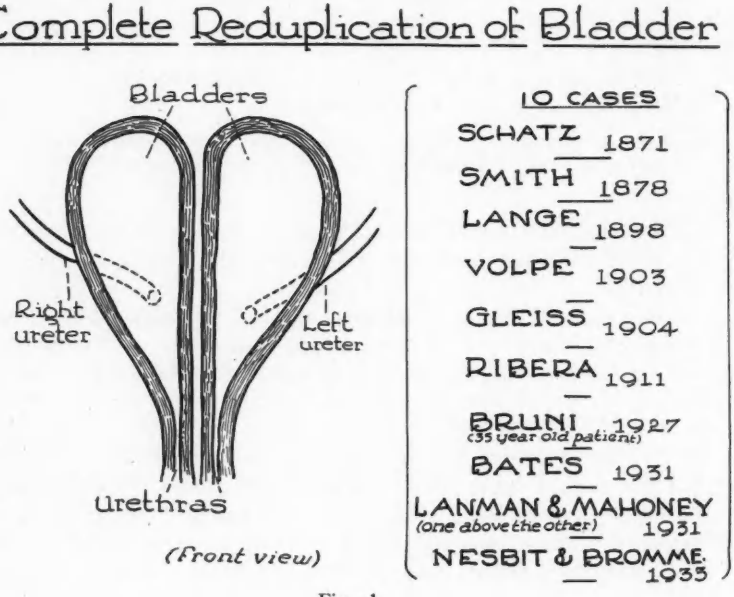


Fig. 1.

separate urethra. There was no communication between the two vesical cavities and the right bladder contained a calculus. This was an autopsy specimen.

3. (1898 Lange reported a case of complete reduplication of the bladder, each bladder with one ureter emptying into a separate urethra. There was a double penis and a double raphe on the scrotum; there were two anal folds and depressions with atresia of both ani. This was a stillborn specimen.

4. (1903 Volpé reported a case of a stillborn child with complete reduplications of the bladder, penis, and colon. The right colon emptied into the right bladder and the left colon into the left bladder. There was also a horseshoe kidney and one ureter.

5. (1904) Gleiss described a specimen of complete reduplication of the bladder in a female stillborn with reduplication of the urethra, vagina, labia majora, anus, and anal folds.

6. (1911) Ribera reported complete reduplication of the bladder associated with reduplication of the penis, one penis being just above the other.

7. (1927) Bruni reported complete reduplication of the bladder in

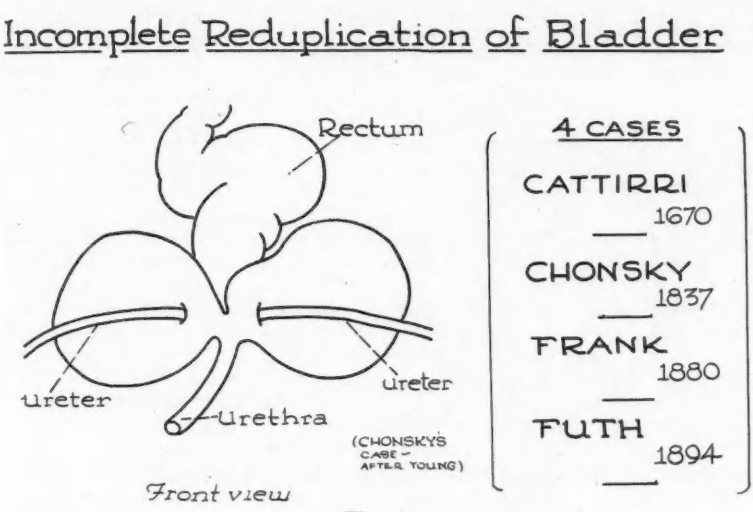


Fig. 2.

a thirty-five-year-old man who had two penes, a widely cleft scrotum, and two anal orifices. The two bladders were independent. On each side there was a single kidney whose ureter led to the homolateral bladder.

8. (1931) Bates described a case of complete reduplication of the bladder in a stillborn infant. There were separate, single kidneys, each with a single ureter which drained into the homolateral bladder. Each bladder had its separate urethra, and there were two vaginas and two vulvas each with separate labia and clitoris, but only one anus was present.

9. (1931 Lanman and Mahoney reported a case of complete reduplication of the bladder with one bladder above the other, the lower one being exstrophic. There were two penes, both with hypospadias, and two scrota. The urethra in the right penis joined the upper bladder and was patent. A probe could not be passed through the left penis. A cystogram of the upper part of the bladder showed a reflux up the right ureter. Excretory urograms showed a small amount of dye in the right renal region.

10. (1933) Nesbit and Bromme reported a case of complete redupli-

cation of the bladder with a double penis on a single stalk bearing two urethras, going separately to the right and left bladders. The kidneys were normal and each emptied by a single ureter into the respective bladder. The patient voided two streams and was continent of urine.

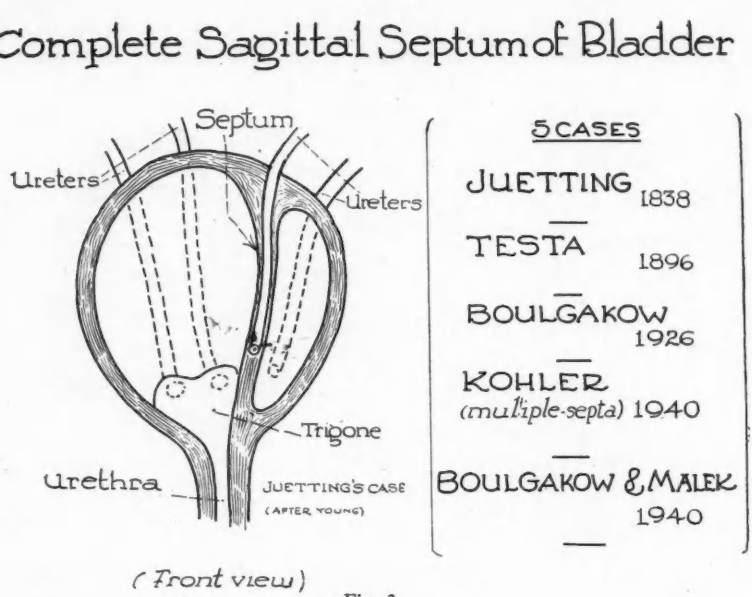


Fig. 3.

GROUP II—INCOMPLETE REDUPLICATION OF THE BLADDER (FIG. 2)

11. (1670) Cattirri reported an autopsy case of incomplete reduplication of the bladder (vesica duplex) in a fifteen-day-old-infant in whom the two bladders were separated from one another by the rectum. The bladders entered a common urethra and each received one ureter.

12. (1837) Chonsky described an autopsy specimen of incomplete reduplication of the bladder (vesica duplex) similar to that of Cattirri in which the rectum separated the two halves, one ureter emptying into each bladder cavity. The two cavities were drained by a common urethra.

13. (1880) Frank described an autopsy specimen of incomplete reduplication of the bladder with a right and left compartment; one ureter opened into each compartment and both halves of the bladder communicated with a single urethra.

14. (1894) Futh reported an autopsy case of incomplete reduplication of the bladder with a right and left cavity into each of which a single ureter emptied. The two cavities communicated just above the trigone. A patent urachus was associated with the left chamber.

GROUP III—COMPLETE SAGITTAL SEPTUM OF THE BLADDER (FIG. 3)

15. (1838) Juetting reported an anatomical specimen in a monster with a complete septum of the bladder (vesica bipartita). A complete sagittal septum divided the bladder into two parts; the large cavity on the right contained the trigone with two ureteric orifices and communicated with the urethra. A third ureter entered into the septum and a fourth ureter into a smaller, completely closed, loculus on the left.

16. (1896) Testa reported a case of complete septal bladder with a complete sagittal septum dividing the bladder into two compartments and a ureter emptying into each loculus. There was no description of the urethra but apparently this case is similar to that of Boulgakow and Malek (Case 19).

17. (1926) Boulgakow reported a case of complete septal bladder in which a sagittal septum extended to the inferior layers of the triangular ligament. Each vesical chamber received one ureter.

18. (1940) Kohler reported a case with multiple complete septa dividing the bladder into many loculi. The patient was a 12-day-old infant who died of uremia. Bilateral polycystic kidney, cryptorchidism and perineal hypospadias also were present.

19. (1940 Boulgakow and Malek described an autopsy specimen of complete septal bladder with a sagittal septum dividing the bladder into a small closed compartment on the right and a large main cavity on the left which communicated with the urethra. There was a huge double kidney on the right; the ureter from the upper right kidney emptied into the lower trigonal area of the main bladder. The ureter from the lower right kidney emptied into the upper portion of the small closed bladder cavity on the right; the left ureter emptied into the larger bladder cavity, entering on the trigone opposite the ureter from the right kidney.

GROUP IV—INCOMPLETE SAGITTAL SEPTUM OF THE BLADDER (FIG. 4)

20. (1656) Blasius reported an incomplete sagittal septum dividing the bladder into two lateral chambers communicating anteriorly near the internal vesical orifice (an autopsy specimen).

21. (1860) Scarenzio reported an incomplete septal bladder in a nineteen-year-old man who died of peritonitis. There was a sagittal septum which was incomplete anteriorly so that the ureters opened below the septum and communicated with a single urethra.

22. (1898) Muller reported a case of incomplete sagittal septum, the two halves of the bladder uniting near the urethra; a single ureter entered into each bladder cavity.

23. (1904) Kermauner reported a case of a stillborn child in which a complete saggital septum divided the bladder into two chambers which communicated near the internal vesical orifice. A single ureter emptied into each chamber.

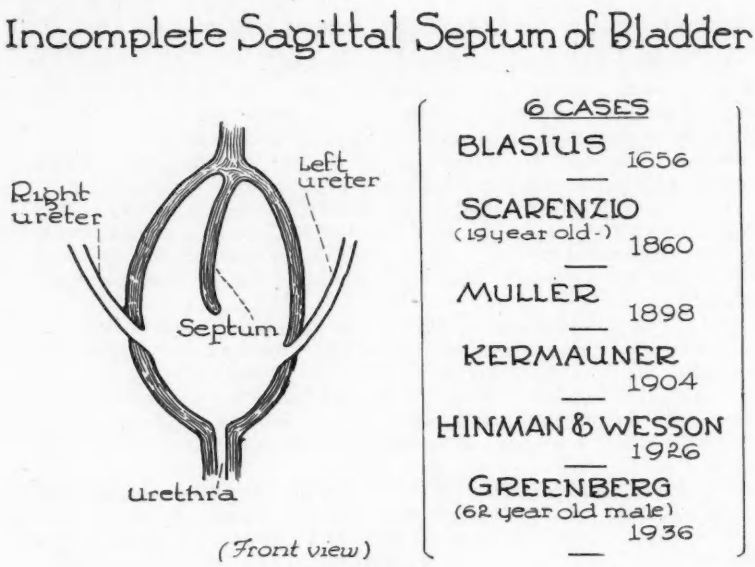


Fig. 4.

24. (1926) Hinman and Wesson described an incomplete septal bladder in a sixty-six-year-old man with urinary obstruction due, for the most part, to a markedly hypertrophied interureteric bar. The septum, which was sagittal, divided the bladder into two halves. The case was treated by excision of the septum and interureteric bar and a portion of the trigone. The patient recovered.

25. (1936) Greenberg reported a case of incomplete septal bladder in a sixty-two-year-old man seen at autopsy. There was a sagittal septum dividing the bladder into right and left compartments with a small communication near the internal sphincer. There was a calculus in the left compartment and the bladder mucosa was necrotic and gangrenous. No description of the ureters was given.

GROUP V—COMPLETE FRONTAL SEPTUM OF THE BLADDER (FIG. 5)

26. (1927) Michelson reported a case of complete septal bladder with a frontal septum forming a closed chamber into which one ureter of a double right kidney emptied.

27. (1933) Edwards described an autopsy specimen of complete septal bladder in a 1-day-old infant. The bladder was divided into two chambers by a frontal septum. The right ureter emptied into the anterior chamber which communicated with the urethra. However, there

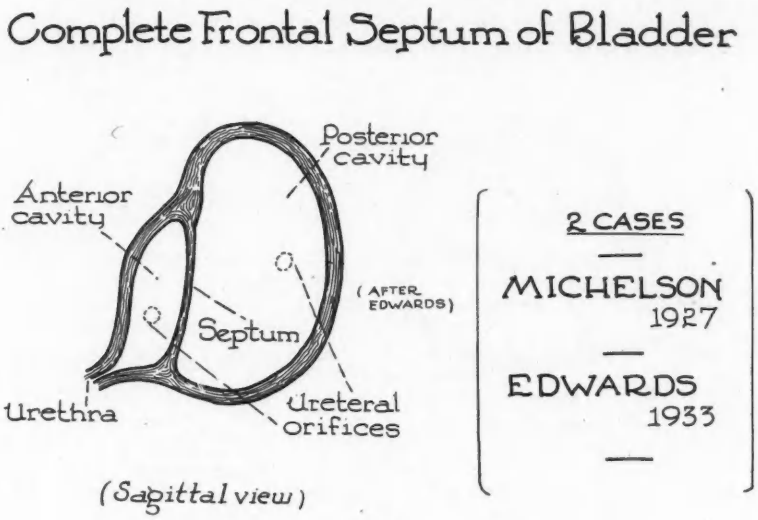


Fig. 5.

was a stenosis of the ureteral orifice and moderate right hydronephrosis. The posterior chamber was completely closed and a markedly dilated, tortuous left ureter emptied into this loculus.

GROUP VI—INCOMPLETE FRONTAL SEPTUM OF THE BLADDER (FIG. 6)

28. (1903) Cathelin and Sempé described an autopsy specimen of incomplete septal bladder with a frontal septum dividing the bladder into anterior and posterior chambers. The patient was an eighty-two-year-old-man. The right ureter opened into the anterior chamber and the left into the posterior chamber.

29. (1920) Caulk reported two surgical cases of incomplete septal bladder, one in a forty-year-old man who had a small fibrous frontal septum 3/8 inch behind the interureteric bar. The septum projected a 1/2 inch above the trigone, dividing the bladder into two pouches. It extended to the posterior wall of the bladder and was treated by excision.

30. The second case in a forty-two-year-old woman was also a frontal septum. It was situated about one inch above the trigone, com-

pletely crossing the base of the bladder and fanning out on each side to the wall of the bladder. The ureters emptied into the lower chamber. The septum was excised, together with a portion of the posterior bladder wall.

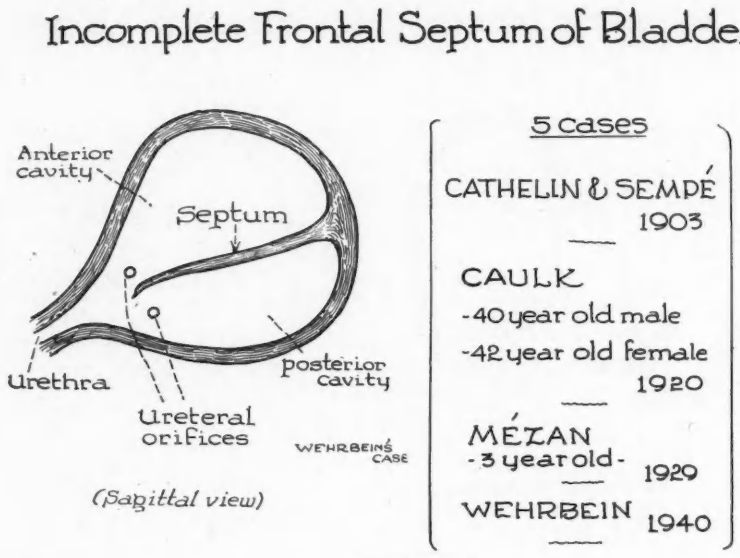


Fig. 6.

31. (1929) Mézan reported an incomplete septal bladder in a child three years of age with a frontal septum dividing the bladder into anterior and posterior chambers which communicated near the internal vesical orifice. The left ureter emptied into the anterior compartment whereas the right ureter terminated as a blind cystic loculus in the posterior bladder wall (referred to as vesica tripartite).

32. (1940) Wehrbein reported a case of incomplete septal bladder with a frontal septum dividing the bladder into anterior and posterior chambers. Thre was a double right kidney with two ureters. The upper right kidney was atrophic and communicated through a dilated, tortuous ureter with an almost completely closed posterior chamber. The lower right kidney with a normal ureter and left ureter emptied on the septum into the larger anterior chamber which communicated with the urethra. The surgical treatment for this case was carried out in two stages. Right ureterostomy and excision of the septum were done following right heminephrectomy and ureterectomy.

We wish to add to this collection a case which, after very careful consideration, we elect to class as incomplete reduplication of the bladder rather than incomplete septum.

CASE REPORT

A white female infant, No. 26641, aged ten weeks, was admitted to the hospital September 9, 1944, with chills and fever and a large mass in the lower abdomen.

The history obtained from the mother was that the child appeared well up to the age of three weeks at which time a mass was noted in the lower abdomen. About the time the mass appeared, the child began to have chills and fever up to 103 F. From that time until admission to the hospital seven weeks later, there were repeated atacks of chills and fever and the mass in the lower abdomen had gradually increased in size.

Examination revealed a rather sick looking child, weighing 9 pounds and 10 ounces. The skin and mucous membranes indicated a rather marked degree of anemia. The remainder of the examination revealed no positive findings except in the lower abdomen where a large pyriform mass, most prominent in the midline and extending up to the navel, could be seen. The mass was dull on percussion and firm on palpation, giving the effect of a distended bladder. It could be moved from side to side. A catheter was inserted and 8 ounces of purulent urine obtained. The mass became smaller but did not entirely subside. Examination of the catheterized specimen of urine showed Gram-negative bacilli and the cultures showed B. coli aerogenes which did not split urea.

The red blood count was 1,600,000; hemoglobin, 30 per cent; white blood cells, 12,200; neutrophils, 66 per cent; and small lymphocytes, 44 per cent. The carbon dioxide combining power was 18 volumes per cent and the nonprotein nitrogen was 40 mg. per 100 c.c. blood. Blood transfusions and fluids were administered and alkalinization instituted until the fluid balance was restored.

Plain roentgenograms of the kidneys, ureters and bladder revealed no stones but the first intravenous urograms were unsatisfactory.

Cystoscopy was carried out under general anesthesia. Just back of the internal urethral orifice, which appeared normal, could be seen the margin of the septum which divided the bladder into anterior and posterior chambers. The anterior chamber was carefully studied, and no ureteric orifices could be seen. The cystoscope was then passed into the posterior pouch which contained a large amount of purulent urine requiring considerable irrigation to wash it clear. Examination of this chamber showed a considerable amount of trabeculation similar to that seen in bladder neck obstruction. There were two ureteric orifices and the trigone appeared to be normal. Spurts of urine could be seen coming from the left orifice but none from the right. Attempts to catheterize the right orifice were unsuccessful as the catheter could not be

inserted for a distance of more than 1.5 cm. The left ureter could be catheterized with ease; little stasis was found in the left renal pelvis. A specimen collected from the left kidney showed the same type of infection as that found in the bladder.

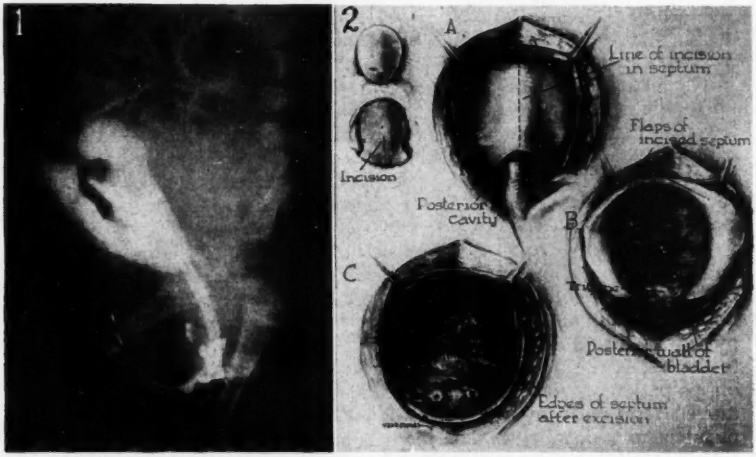


Fig. 7. Case 26641. *(1)* Retrograde cystogram shows septum with two fairly well defined separate bladder chambers. *(2)* Septum incised shows posterior chamber of bladder.

A retrograde cystogram demonstrated the septum seen on cystoscopic study and two fairly well defined separate bladder chambers (Fig. 7, *1*). The cystoscopic impression was that we were dealing with an incomplete reduplication of the bladder and probable congenital absence of the right kidney. Subsequent intravenous urograms showed the presence of a fairly normal left kidney but no dye could be seen on the right side.

After adequate preparation, operation was performed under drop-ether anesthesia on September 27, 1944. A midline suprapubic incision was made. After the bladder was exposed, the peritoneum was opened and the pelvis carefully examined. Two ovaries were seen but the uterus could not be felt. A fairly large kidney was felt in the left renal fossa but none in the right. Palpation of the bladder revealed two distinct pouches with a deep cleft separating them, as indicated by the preoperative cystogram. The peritoneum was then closed with a double layer of sutures and the bladder opened. The anterior chamber was slightly smaller than the capacity of the normal bladder at that age. Just back of the internal urethral orifice the opening to the posterior chamber could be seen. With the index finger inserted through the opening,

which looked considerably like the opening of a diverticulum, the septum was incised so that the poserior chamber came into full view (Fig. 7, *2*). The entire septum was then removed and the margins of the mucous membrane approximated with catgut sutures to control bleeding. A whistle-tipped catheter was inserted as a suprapubic tube and the bladder closed in layers. The wound was treated with alcohol and ether, and closed in layers with a Penrose tube to the lower angle.

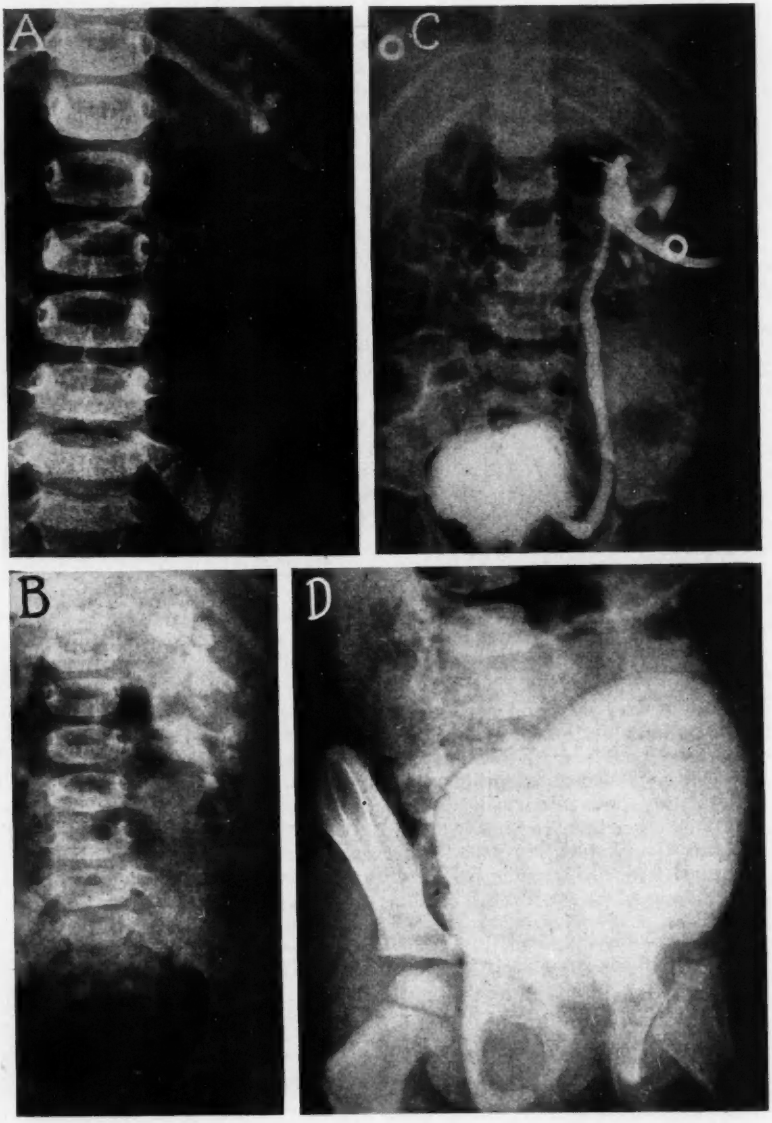
The postoperative condition was considered good. The suprapubic catheter was removed on the fourteenth postoperative day and a retention urethral catheter inserted to facilitate closure of the wound. The patient was discharged from the hospital on the twenty-second postoperative day at which time her general condition was satisfactory. The administration of urinary antiseptics, chiefly sulfanilamide and sulfadiazine and penicillin, started in the postoperative period was continued after the infant was discharged from the hospital.

Interval postoperative examinations showed satisfactory gain in weight but the urine continued to be heavily infected. Periodic roentgenograms showed no stones up to June, 1945, eight months after the operation when multiple stones appeared in the calyces of the solitary left kidney (Fig. 8, *A*). Intravenous urograms revealed good function of the left kidney and a fairly normal calyceal pattern wih the exception of a moderately dilated calyx in the upper pole (Fig. 8, *B*) of the left kidney.

On November 14, 1945, the stones were removed from the kidney and the upper pole was resected in order to remove the portion carrying the dilated calyx (Fig. 8, *C*). A No. 18 whistle-tipped catheter was inserted through the lower pole to the pelvis as a nephrostomy tube. The postoperative condtion was considered satisfactory, and the baby made a normal postoperative recovery.

The urinary infection persisted for some months but under the combined administration of penicillin and sodium sulfathiazole, the urine, at least at the time of the last examination on June 3, 1946, was free of infection. Roentgenograms on that date showed a small shadow in one of the upper minor calyces whtich was probably a stone left at operation rather than one newly formed. Cystograms showed a cleft separating the bladder into two incomplete pouches after removal of the septum (Fig. 8, *D*). The baby's present weight at twenty-one months is 26 pounds.

In this case the known developmental anomalies were: (1) presence of an external cleft and a septum which divided the bladder into narrowly communicating anterior and posterior compartments; (2) arrest of the right ureter and absence of the right kidney. There is a possibility also that the uterus was absent or deficient. Although both ovaries were thus recognized, the uterus could not be detected by digital exploration. The association of


A
C
B
D

anomalies of the bladder and ureter probably arises through the developmental interdependences of these structures; absence of the kidney is to be explained by the arrest of the ureter. Involvement of the ureter and kidney represents so common a defect that its developmental history has become widely familiar. Division of the bladder, whether in the form of a septal partitioning, a separation into two independent pouches, or their combination as in this case, is so rare and little known that a brief discussion of its embryological origin is offered.

The critical period in the formation of the bladder, insofar as it concerns the stages of development in which aberrancy produces a defect of the type here described, is in the fifth through the seventh weeks. Prior to this time the terminal segment of the gut is the cloaca, an xpanded chamber which ends blindly in contact with the perineal wall. The allantois is extended from the cloaca ventrally. The cloaca soon undergoes subdivision.

Division of the cloaca is accomplished by the extension of the cloacal septum, an infolding of the epithelial wall of the cloaca enclosing a band of mesoderm which carries within it a short pocket of the peritoneal cavity(Fig. 9). Extension of the cloacal septum progresses, and during the seventh week the rectum is sheared completely from the ventral portion of the cloaca. This ventral division represents the bladder and urethra, the allantois being prolonged from its craniel extremity to the umbilicus. The defined walls of all these structures represent epithelium alone. The immediately surrounding mesoderm, including that of the cloacal septum, differentiates into muscle, connective tissue, vessels, and the peritoneum of the regions directly related to the body cavity.

A specific deviation from the course of normal development may be postulated in explanation of the anomalous bladder here reported. It is apparent that a supernumerary cloacal septum was formed, its behavior being comparable to that of the normal cloacal septum which separates the rectum and bladder. In indenting the epithelial wall of the bladder, this septum carried an evagination of perito-

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Fig. 8. (opposite page) Case 26641. *(A)* Check-up roentgenogram (June 1945) shows multiple stones confined to calyces of solitary left kidney. *(B)* Intravenous urogram (June 1945) shows moderately dilated calyx in upper pole. *(C)* Postoperative pyelo-ureterogram through nephrostomy tube. Dilated upper calyx removed. *(D)* Postoperative cystogram (June 3, 1946) done under anesthesia, bladder overdistended. Note cleft separating bladder into two incomplete pouches.

neum, as evidenced by the cleft between the two pouches. The solid extension of the septum was converted into smooth muscle and connective tissue. In this case the plane of the abnormal septum was such as to divide the bladder into anterior and posterior compart-

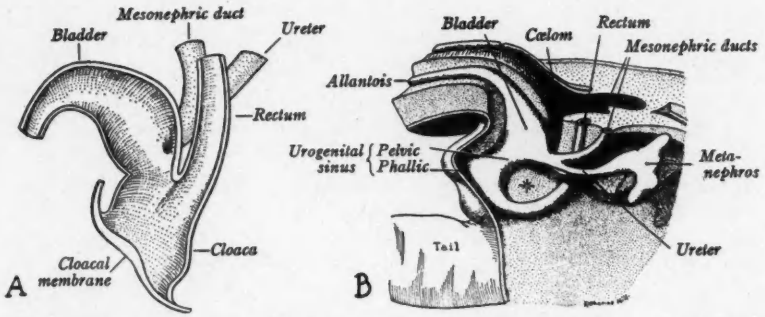

Fig. 9. Two stages in division of cloaca, viewed from left side. *(A)* Embryo 8 mm. long. *(B)* Embryo 11 mm. Asterisk marks cloacal septum (uro-rectal septum). (Courtesy of Leslie B. Arey and the W. B. Saunders Co.)

ments, thus corresponding to the plane of the normal (uro-rectal) septum.

The series of reported cases presents wide variety in the character of the divisions of the bladder, with regard both to the plane of division and the degree of separation of the two components. It may be conjectured that all are of fundamentally the same origin, associated with aberrant cloacal septa of correspondingly diverse positions and extents. The etiology of such abnormality in the individual case usually must remain unknown, since it is rarely possible to determine the factor or factors which may have so disfavored the embryo as to produce maldevelopment. However, it should be recalled that the cloacal region as a whole undergoes a complex transformation; interference with its progress may produce not only arrest (that is, persistent cloaca, anal atresia) but also redundancies such as accessory septums which partition the bladder.

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DISCUSSION

DR. GEORGE F. CAHILL (New York, N. Y.): I wish to make a few remarks about Dr. Hamm's paper on amicrobic pyuria. The established fact for diagnosis is first, pyuria; second, no demonstrable bacteria by ordinary stains on smears; no demonstration of acid-fast bacteria by carbol fuschin, and no growth either aerobically or anaerobically on the usual medias. In addition, as shown by Widboltz, patients apparently recover with arsenamides.

Because of similarity to the attempts to find the cause of syphilis, before the discovery of the Spirocheta pallida, we did dark-field illumination examinations to see if any stain-resistant organisms were present. Our examinations disclosed none. We also did special stains on biopsies from the bladder to see if any inclusion bodies or protozoa were present, but we were unable to find any. The disease is suspected of being due to a virus, but I do not know of any work that has supported this suggestion.

SECOND DAY, JUNE 21, 1946

BILATERAL PELVIC AND URETERAL DUPLICATION WITH URETERINE ECTOPIC URETER

ALEXANDER B. HEPLER, M.D.
Seattle, Washington

It is not my purpose to discuss in detail the subject of ureteral ectopia. This has been done repeatedly in numerous articles and statistical studies.* The pertinent facts, both anatomic and clinical, have been recognized and are well known.

However, I should like to report one of the three cases I have had, because several of its features are of sufficient interest to be recorded. The other two conformed to type, that is females with diurnal incontinence independent of normal urination; unilateral pelvic and ureteral duplication with the ureter from the upper segment ectopic, in one emptying into the urethra and in the other into the hymenolabial sulcus; sufficient function in the abnormal segments to excrete indigo carmine to permit location of the ectopic openings; the condition corrected in one by heminephroureterectomy and in the other by nephroureterectomy.

The unusual features of the third case which suggested its presentation were: (1) The extent of the upper urinary tract anomaly with destruction of three-quarters of the renal mass—there was a bilateral pelvic and ureteral duplication with hydronephrotic destruction of both halves of the right kidney and the upper half of the left, the ureter from which terminated in the cervix of the uterus, yet this youngster was in vigorous health both before and after operation. (2) The impossibility of demonstrating the abnormal segments of the kidneys by urography either excretory or retrograde—this made the diagnosis difficult and largely a matter of deduction. (3) The unusual location of the ectopic ureteral orifice, in the cervix of the uterus, which brings up controversial embryologic consideration. (4) The method of treatment.

*Those references marked by an asterisk in the bibliography contain detailed discussion of ureteral ectopia.

CASE REPORT

A girl, five years old, was referred because she was constantly wet regardless of normal urination. This suggested an ectopic ureteral orifice, and the examination was made with this in mind. The child was healthy and well and there were no abnormal findings of importance on general examination. Phenolsulphonephthalein output was 68 per cent in two hours with the peak of elimination in the first hour. Blood values for urea and creatinine were normal.

Excretory urograms showed a left pelvis situated lower in the kidney than normal with a slight compression deformity of the upper major calyx (Fig. 1). However, there was no opaque medium visible in the upper third of the left kidney to indicate a pelvic duplication and none at all on the right side, except a very faint diffuse shadow in the thirty-minute film.

On cystoscopy the left ureter was catheterized but no ureteral opening could be found on the right. Indigo carmine injected intravenously appeared in good concentration through the left catheter but there was none in the bladder after thirty minutes. A pad placed on the child during the examination was moist but there was no color. Examination of the external urethral meatus and vestibule, the usual site of ectopic orifices in the female, showed no abnormalities. The retrograde pyelogram was essentially the same as the excretory (Fig. 1).

These findings, that is the very faint shadow on the right in the excretory urogram after thirty minutes and the absence of indigo carmine in the bladder after the left ureter had been catheterized, seemed sufficient evidence to warrant the conclusion that there was an advanced right hydronephrosis with an extravesical ureteral orifice, but not enough function to excrete either diodrast or indigo carmine, to demonstrate the anomaly or locate the abnormal opening.

At operation, February 24, 1945, an almost completely destroyed double right kidney with two enormously dilated ureters was found and removed. The pathologist, Dr. Paul Lund, Swedish Hospital, reported as follows:

Gross description: "Specimen consists of an enlarged, irregular lobular kidney with a double pelvis and double ureter. Only a small shell of kidney parenchyma remains due to the presence of cystically dilated calyces. Both pelves and both ureters are enormously dilated. The inferior ureter measures 2.5 cm. in diameter. The mucosa covering both pelves shows the presence of small, hemorrhagic areas. The gross picture is that of a complete hydronephrotic atrophy associated with double pelves and ureters."

Histology: "Sections taken through the remaining kidney parenchyma show it to be markedly distorted in a hydronephrotic atrophy and diffusely infiltrated by chronic inflammatory cells associated with large amounts of fibrous connective tissue. The latter process is that of a chronic pyelonephritis. Sections takeu through the pelvic epithelium as well as the ureter show a similar inflammatory process. Diagnosis:

Pelvic and ureteral duplication with megaloureters. Hydronephrosis, Grade IV, in both segments. Chronic pyelonephritis."

I was confident that the opening of one or both of these ureters was extravesical, because they could not be demonstrated in the bladder and that therefore the child would be dry. However, after operation she was just as wet as before.

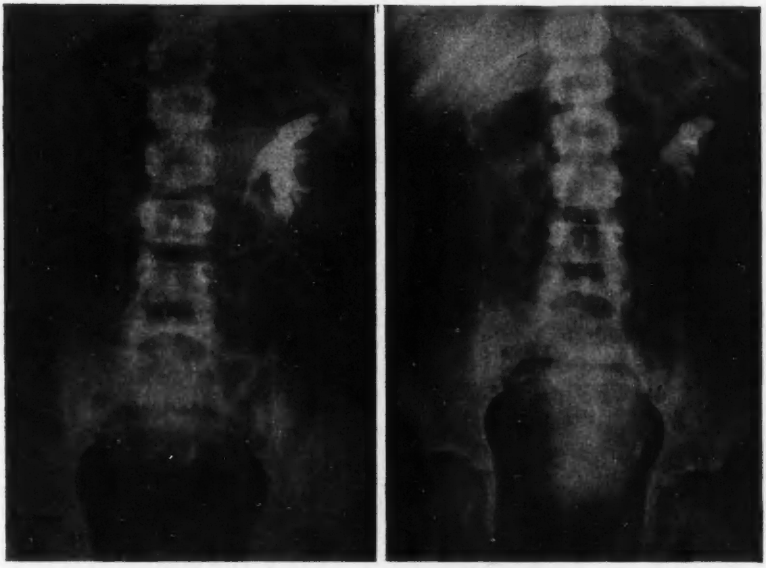

Fig. 1. *(A)* Retrograde pyeloureterogram of lower normal left segment with slight downward displacement of upper calyx by hydronephrotic upper segment. *(B)* Excretory urogram shows very faint shadow on right, as only indication of hydronephrotic renal segments in bilateral pelvic and ureteral duplication.

Attention was then shifted to the left kidney. The low position of the pelvis in the renal mass (Fig. 1) and the slight compression deformity of the upper calyx was fairly conclusive evidence that there must be a double kidney on the left also, with destruction of the upper half whose ureter had an ectopic opening. Here again the function of the segment was so poor that it would not excrete diodrast for x-ray purposes nor indigo carmine to demonstrate the abnormal termination of the ureter.

Renewed search was then made under rectal sodium pentothal anesthesia. The vagina was explored through a Kelly endoscope. The cervix was reddened and irritated and there was a granulomatous nodule on the

left margin of the external os. The cervix was moist and when dried off, urine could be seen seeping from the external os. The seepage could be increased by bimanual pressure in the left flank. After one-half hour, about 2 c.c. of urine collected in the upper vagina.

Attempts to catheterize the opening in the cervix were unsuccessful because of the difficulty in controlling the direction of the tip of the

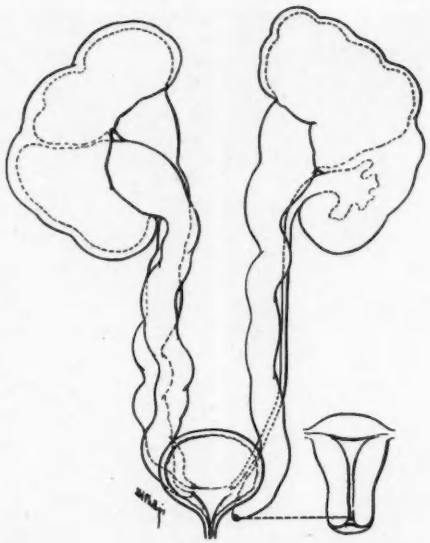

Fig. 2. Diagrammatic representation of anomalies found at two operations. Ureter from normal lower left segment was closely adherent to dilated accessory ureter throughout.

catheter through the Kelly endoscope. Also a granulomatous nodule in the external os of the cervix of a five-year-old child does not make much of a target. It probably could have been done with the flexible metal guide which Crenshaw has devised for catheterization of aberrant vaginal ureters and ureterovaginal fistulas.

However, there was sufficient evidence now to warrant the diagnosis of a double left kidney with a hydronephrotic uper half whose ureter opened into the cervix.

This was confirmed at operation (November 10, 1945). There was no sharp demarkation between the blood supply of the cephalic and caudal segments of the kidney, and the pedicle was distorted by the dilated pelvis and ureter from the hydronephrotic upper half (Fig. 2).

Because the lower half was the only kidney tissue this child had left, the risk of a heminephrectomy was too great, so a complete ureterectomy was done beginning just at the renal pedicle and ending where the ureter passed under the broad ligament to enter the cervix. The diseased ureter was clamped just at the lower margin of the pedicle, transfixed and doubly ligated with cotton. The upper portion was re-

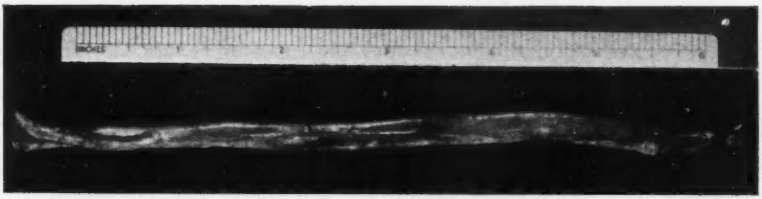

Fig. 3. Excised extravesical ureter

moved through a lumbar incision and the lower half through a left rectus incision with extraperitoneal approach (Fig. 3).

The accessory ureter had to be dissected from the normal one throughout its entire length, but this was facilitated by the fact that the normal ureter had been catheterized prior to operation. The pathologist, Dr. Lund, reported as follows:

Operative specimen submitted: "Left extravesical accessory ureter."

Gross description: "Specimen consists of a large, thick-walled ureter measuring 24 cm. in length, 1 cm. in diameter. On section, the wall is extremely fibrous in character and measures 4 mm. in thickness. The mucosa shows small, pin-point hemorrhagic areas over the surface."

Histology: "Sections show small areas of ulceration of the lining mucosa with a diffuse, subepithelial infiltration by chronic inflammatory cells. The wall is fibrous in character. Diagnosis: Hydro-ureter with chronic ureteritis."

There was a postoperative left lung atelectasis which was relieved by bronchoscopy, and the child is now well and dry.

DISCUSSION

Embryologic considerations.—An ectopic ureter opening into the uterus is a rare anomaly, in fact its possibility is denied by some observers. Abeshouse in 1943 reviewed and tabulated four cases collected by Thom and added one of his own. Several other cases have been reported but rejected in the tabulation, because of indefinite and inconclusive evidence.

In four of the five cases the ectopic openings were in the cervix. In Abeshouse's case, the right ureter from a sigmoid kidney emptied into the fundus of the uterus. This was found at autopsy in a thir-

teen-month-old child who had other developmental defects, such as cloacal anomaly with partial atresia of the vagina and a vesicovaginal fistula.

Bicornuate uteri were present in three of the other patients. In two of the five the condition was found at autopsy, and in two, inadvertently during a laparotomy. The conditions in Kudji's patient more nearly resemble those found in mine in that the anomaly was observed clinically, the uterus and the tubes were normal, and a partial ureterectomy was done with cure.

It seems that there has been undue skepticism about the possibility of ectopic ureters emptying into the uterus and the vagina proper, simply because the latter are Müllerian duct derivatives while the ureter arises from the Wolffian duct. The distinction is made here between the vagina proper, a Müllerian system derivative and the vestibule, which is of Wolffian origin. The latter is the site of the majority of ectopic ureteral openings in the female.

With due allowances for careless observation, faulty nomenclature, and the fact that with the disappearance of the hymen and in multipara, what was a vestibular orifice may seem to be vaginal, there are still a large number of authentic reports of ectopic openings in the Müllerian portion or upper vagina.

Deming in 1934 before this Society, reported one in the anterior fornix of the vagina and reviewed twenty-two authentic cases. Thom six years before that had collected thirty-two cases of vaginal openings in distinction to the vestibular, of which he found forty-five. Eisendrath in 1938 added thirteen to the vaginal and thirty to the vestibular making a total of forty-five and seventy-five, respectively. There have been quite a few cases reported since.

Wesson states: "The statement has been repeatedly made that from the standpoint of development it is impossible for a ureter to open into the vagina. We are inclined to question on embryologic grounds all reports of ureters opening into the vagina, but when the cystoscopist has succeeded in passing a catheter through a vaginal fistula and has made a pyelogram of the kidney, then it must be true." He then cites a number of cases in which this has been done. In other words, its impossibility, on embryologic grounds, cannot be insisted upon, when it actually occurs and can be demonstrated clinically.

Yet I think the statement that it is an embryologic impossibility,

has been too much taken for granted and handed down without thorough analysis. It is conceded that direct connections between the Wolffian and Müllerian systems in their earlier formations would result in gross embryologic abnormalities such as those reported by Moller and Ahlfeld which are not pertinent to this discussion. However, there appears to be a perfectly feasible explanation and the answer lies in the fate of the Wolffian duct in the female.

The ectopic ureter arises from the Wolffian duct, and is carried with it and implicated in its terminations outside the bladder. In the male the Wolffian duct becomes the epididymis, vas, seminal vesicle and ejaculatory duct and the implicated ureter may empty into any of these structures. Thom collected seventeen cases in which the extravesical ureter emptied into the seminal vesicles, six into the vas deferens and five into the ejaculatory ducts. Culver and Hamer each reported before this Society such a termination.

In the female, the caudal end of the Wolffian duct aids in the formation of the vestibule of the vagina, and the remainder of it extends from this point to the parovarium or organ of Rosenmuller in the broad ligament. In its course, it passes along the anterior wall of the vagina, then in the lateral wall, passes through the muscularis of the cervix to the level of the internal os and then into the broad ligament to the parovarium. By the beginning of the third month, the duct has become a vestigial structure, but the uterine and vaginal segments may persist as Gärtner's ducts. This occurs in about one-third of all females. Several cases have been reported of the persistence of the entire Wolffian duct and it has been implied in a number of other cases that have not been definitely proven.

Since the ectopic ureter is implicated with the terminations of the Wolffian duct in the female, just as it is in the male, it is reasonable to assume that it may empty, not only at the ducts' caudal extremity in the vestibule, but anywhere along the remnant line in the vagina and cervix of the uterus, that is anywhere along the course of Gärtner's duct.

This assumption may be made clearer by a brief review of the steps in the development of extravesical ureteral openings.

There is agreement in a general way about the embryologic variation which results in the double kidney or pelvic and ureteral duplication (Fig. 4, *A*). Whether from the splitting or fission of one

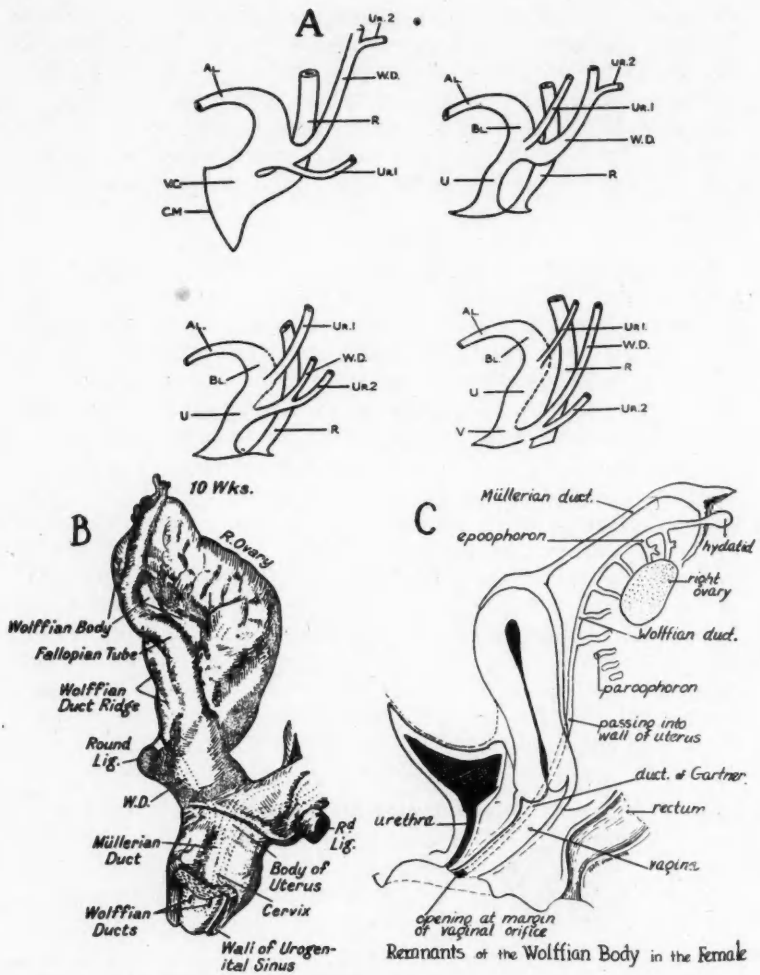

Fig. 4 *(A)* Development of extravesical ureter. When there are two ureteral buds on Wolffian duct, distance between them determines whether both ureters shall open into bladder or one shall have an ectopic opening. This demonstrates how ectopic ureter becomes implicated in ultimate destiny of Wolffian duct, which becomes vas, seminal vesicle and ejaculatory duct in male and vestibule of the vagina and Gärtner's duct in female. (Courtesy of Miley B. Wesson.)
(Continued at bottom of opposite page)

ureteral bud or by the formation of twin buds, eventually there are two ureteral buds attached to the lower end of the Wolffian duct. Ureteral bud No. 1 which becomes the main ureter is situated caudally on the duct, while No. 2 which becomes the accessory ureter, is higher up. When the lower end of the Wolffian duct is drawn into the uro-genital sinus, to aid in the formation of the bladder floor and trigone, the main ureter, or No. 1 reaches the bladder first. In the rapid growth of the bladder, the lower end of this main ureter is drawn cranially and laterally away from the opening of the Wolffian duct. The upper or accessory ureter is drawn into the bladder later by the expansion of the lower ends of the Wolffian duct, so that it occupies a lower and more central portion in the bladder. It does not participate in the cranial and lateral change of position with the development of the bladder.

How far the two orifices are separated in the bladder will depend on the distance separating the origin of the two buds on the Wolffian duct. A high origin of the upper bud will delay its arrival, so that it may not be included in the bladder, but be implicated in the extravesical terminations of the Wolffian duct to which it is attached, that is the ejaculatory duct, seminal vesicle and vas deferens in the male and the vestigial Gärtner's duct and vestible of the vagina in the female. Figure 4, B shows the genital system of a female human fetus in the tenth week of development and the close relation of the lower ends of Müllerian and Wolffian systems. The ends of the Müllerian and Wolffian ducts are shown by stippled lines. Figure 4, C is a diagrammatic representation of the remnants of the Wolffian body and Wolffian duct in the female and shows Gärtner's duct passing through the cervix and the vagina in its course from the organ of Rosenmuller to the vestibule.

It is not difficult to conceive that the accessory ureter which becomes extravesical, and is carried downward with the Wolffian duct can empty anywhere along this remnant line from the hymen through the cervix of the uterus. When the Wolffian duct is entirely obliterated along this line, the ectopic ureter ends blindly. The blind end may become distended and protrude into the vagina.

Fig. 4. (Continued from opposite page.)

(B) Genital system of a female human fetus in tenth week of development shows close relationship of lower ends of Mullerian and Wolffian systems. Ducts are shown by stippled lines. (After Sir Arthur Keith.)

(C) Diagrammatic representation of remnants of Wolffian body and Wolffian duct in female. Gärtner's duct is shown passing through cervix and vagina in its course from parovarium to vestibule. (After Sir Arthur Keith.)

Occasionally they have been interpreted as intraligamentous, retroperitoneal or adnexal tumors.

Gärtner's duct may be patent throughout its entire length or it may be obliterated in some portion with cystic dilatations in others. A number of cases have been reported of ureters emptying into Gärtner's cysts. Fromme reported one in a woman aged twenty-five who was continent until after her first delivery which resulted in a rupture of a vaginal Gärtner's cyst into which the ectopid ureter emptied.

Meyer assumes that when an ectopic ureter empties into the uterus or upper vagina along the line of Gärtner's duct that the communication is made through a rupture from overdistention and primary atrophy from urine. He says that Gärtner's duct which has a blind end is kept patent by urine, becomes overdistended and perforates at any level, but usually in the vagina. It occurs less frequently in the uterus because the uterine musculature offers greater resistance than the vaginal wall. Meyer bases his observations upon his case in which the vagina and Gärtner's duct were separated only by a thin layer of epithelium.

Although Meyer's explanation is ingenious and perhaps applies in some instances, I do not think that we have to call on hydrodynamics and rupture to explain all of these communications. In defects of this sort it does not seem unreasonable to assume that the opening may be developmental, and that there may be an opening of Gärtner's duct anywhere along its course. It is interesting to note that in the reported cases of vaginal ectopic ureter the openings were comparable to the course of Gärtner's duct, that is in the upper vagina they were in the fornices near the cervix, then on the lateral walls and then in the midline, anteriorly, in the lower vagina.

In the case I have reported the cervical opening was indisputable on the clinical evidence despite the inability to catheterize and visualize the accessory ureter.

Diagnosis.—Goyanna and Greene have emphasized the difficulties of diagnosis in duplication of the renal pelvis and ureter, when one or more of the segments of the kidneys are nonfunctioning because of associated pathologic conditions. This was very aptly demonstrated in this case, in which three of the four segments were nonfunctioning and there was only a suggestion of a very faint shadow on excretion urography to indicate the possibility of a right kidney.

At the first examination the situation on the left side should have been noticed, that is the elongated renal shadow with no demonstrable pelvis from the upper third, and the slight compression deformity of the upper calyx of the visualized pelvis. However, the inability to demonstrate a right ureteral orifice on observation and chromocystoscopy, together with the faint excretion shadow, led to the hasty conclusion that there was a right kidney whose ureter had an ectopic opening. Where the two ureters found at operation,ended is still undetermined, but they were probably intravesical but obliterated by inflammatory contracture and fibrosis.

It was only after nephrectomy failed to relieve the incontinence that attention was centered on the left kidney. Here again the functionless segment of the double kidney could not be visualized because of the impossibility of catheterizing the accessory opening in the cervix. However, the presumptive evidence was conclusive and the surgical indications definite.

In Deming's case of ectopic vaginal ureter, he was unable to catheterize the opening in the vaginal vault just above the anterior cervical lip, and because the corresponding segment was functionless, was unable to determine from which side the aberrant ureter came. This was determined only on exploratory operation.

Treatment.—It is unnecessary to review in detail the treatment of ectopic ureters. The surgical indications and methods are numerous as might be expected from the great variety of conditions to be met. These are covered in the many articles on the subject. Ureteroneostomies, that is transplantations to the bladder, bowel, normal ureter or pelvis are contraindicated as operations of election. They may be necessary in the solitary kidney or where a single ureter is ectopic in the presence of bilateral disease. Here attempted conservation is imperative. However, the anomalous segment is usually so badly diseased that elective conservation is unwise and usually futile. Heminephroureterectomy is the operation of choice in the average case and nephroureterectomy when the entire kidney is damaged and the opposite one normal

Deming's is the only other case reported in which a complete ureterectomy alone was done through two incisions. Because he did not know the side from which the ectopic ureter arose, his first incision by necessity was a midline suprapubic intraperitoneal one. For the removal of the upper ureter, he used a right upper

quadrant incision with a transperitoneal approach. In my patient the removal was entirely extraperitoneal.

When the segment of the kidney, drained by the ectopic ureter is originally small, has undergone atrophy and is not infected, Everett recommends ligation and resection of the abdominal portion only. He reviews seven cases from the literature and reports one of his own in which this was done successfully. However if the ureter is dilated as it usually is, the stump may be the source of continued drainage and infection. The removal of the entire ureter is a matter of very little additional surgery. Renal resection should always be done in conjunction with ureterectomy when feasible, particularly when the anomalous segment is large, functioning actively or infected. In my patient the ureterectomy alone was warranted because of the risk of a heminephrectomy of the only remaining renal tissue.

SUMMARY

A case is reported of a five year old girl with bilateral pelvic and ureteral duplication with hydronephrotic destruction of both halves of the right kidney and the upper half of the left, the ureter from which opened into the cervix of the uterus.

The embryologic features of this rare anomaly are discussed, particularly in relation to the disputed true vaginal and uterine ectopic ureteral openings.

The diagnostic problems and the difficulty of radiographic demonstration of the anomalous renal segments and ureters, when the former are practically functionless, are demonstrated.

After a right nephroureterectomy was done, the patient was cured of her incontinence by the complete removal of the ureter to the anomalous segment of the left kidney.

1215 Fourth Ave., Seattle 1, Wash.

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INTUBATED URETEROTOMY: RESULT AFTER FOUR YEARS

DAVID M. DAVIS, M.D.

From the Department of Urology, Jefferson Hospital and Medical School, Philadelphia, Pennsylvania

The purpose of this paper is to show some results of the operation of intubated ureterotomy after periods ranging up to four years. It is not a complete round-up of all cases; for this, time and energy have been lacking, but I hope that such a round-up may be accomplished soon. In regard to my own cases I may say that practically all have been completely successful, and that none can be classified as a real failure. The symptoms have been relieved in every case. In one case, last seen over three years ago, some infection was still present. In another, a light and symptomless bacillary infection persisted for over two years, and then disappeared spontaneously. One patient died after nine days of uneventful convalescence, of a massive pulmonary embolism. In another case of bilateral hydronephrosis in a horseshoe kidney, the patient died of pyonephrosis on the opposite side before the result of the operation could be ascertained. All other cases are symptom-free and have sterile urine.

Figure 1 represents the case of a physician's wife with a good-sized stone in a hydronephrotic left pelvis. The intravenous urogram (Fig. 1, *B*) shows the result six months after operation. Figure 2 shows a case similar except that there was no stone. The intravenous urogram (Fig. 2, *B*) was taken about six months after operation.

Figure 3, *A* represents a stone in the right kidney of a woman. Figure 3, *B* is a pyelogram showing marked hydronephrosis. Figure 3, *C* and *D*, taken eight months after operation, shows the result. Figure 3, *D* demonstrates complete emptying of the pelvis forty-five minutes after the intravenous injection of diordrast.

Figure 4, *A* represents the original condition in the case which has been followed the longest time. The patient was a woman aged twenty-nine. She complained of pain on the right side, and

investigation showed a large functionless calculous pyonephrosis, which, it was obvious, would have to be removed. On the left side we unexpectedly discovered a well marked hydronephrosis, and ureteral narrowing extending over one-third the length of the ureter. This kidney became infected as a result of the pyelogram,

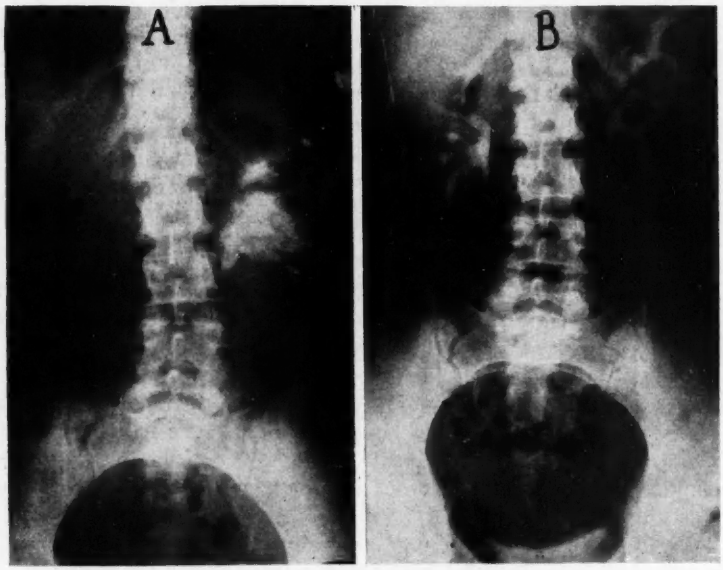


Fig. 1. Case S. K. (*A*) Film taken at time of removal of splint tube. Hydronephrosis and normal ureter are shown. Some of opaque solution has leaked into dressing. *(B)* Intravenous urogram taken six months after intubated ureterotomy.

and made the patient very ill. Operation was therefore performed on the left side. Figure 5 illustrates the procedure. The ureteral narrowing was 12 cm. long. The ureter was split longitudinally for this entire distance, and intubated with a T-tube, as shown. The narrow ribbon of ureter was held close to the T-tube by a few sutures of 000 plain catgut. Figure 4, *B* is an x-ray taken four weeks after operation. The hydronephrosis is still present. The ureter is evidently patent. The stones in the right kidney remain

unchanged. The T-tube was withdrawn immediately after this film was taken.

The patient did well, and a few weeks later the right kidney was removed. The upper ureter was very small, admitting a fine probe with difficulty. This indicates that the obstructive lesions on

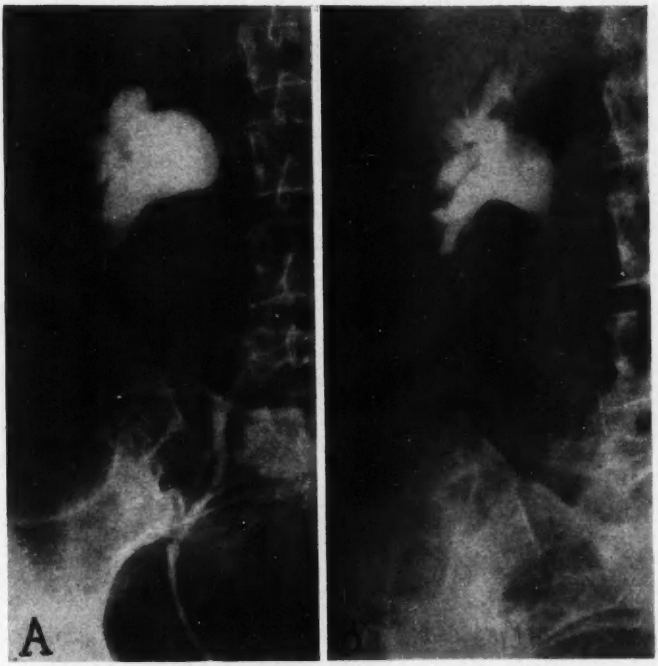


Fig. 2. Case Y. B. (*A*) Hydronephrosis before operation. Note definite ureteropelvic obstruction. (*B*) Intravenous urogram six months after intubated ureterotomy, showing normal ureteropelvic funnel.

the two sides were the same. Six months after the operation on the left kidney an intravenous urogram was made (Fig. 4, *C*). There had been little reduction in the hydronephrosis, but the ureter was evidently well restored and of much greater diameter than before. At this time the patient was prefectly well and the urine sterile. The phenolsulphonephthalein test showed an excretion of

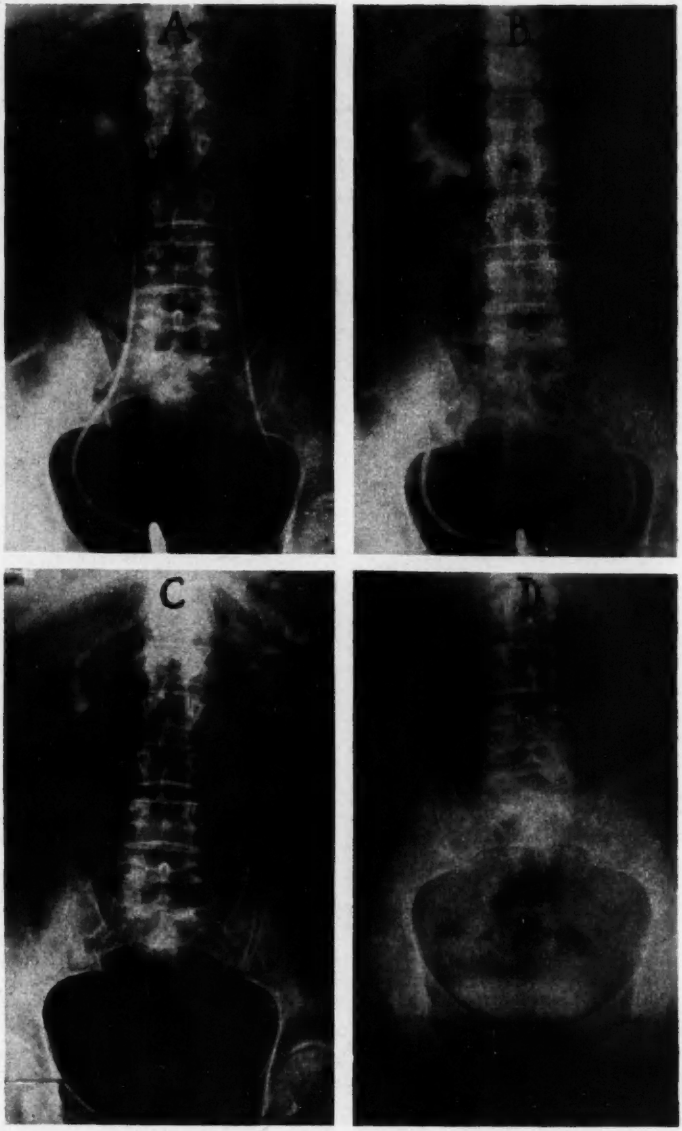


Fig. 3. Case R. K. *(A)* Large stone in right renal pelvis. *(B)* Hydronephrosis and upper ureteral obstruction. *(C)* Intravenous urogram taken eight months after intubated ureterotomy, showing return to normal. *(D)* Film from same series, showing complete emptying at forty-five minutes.

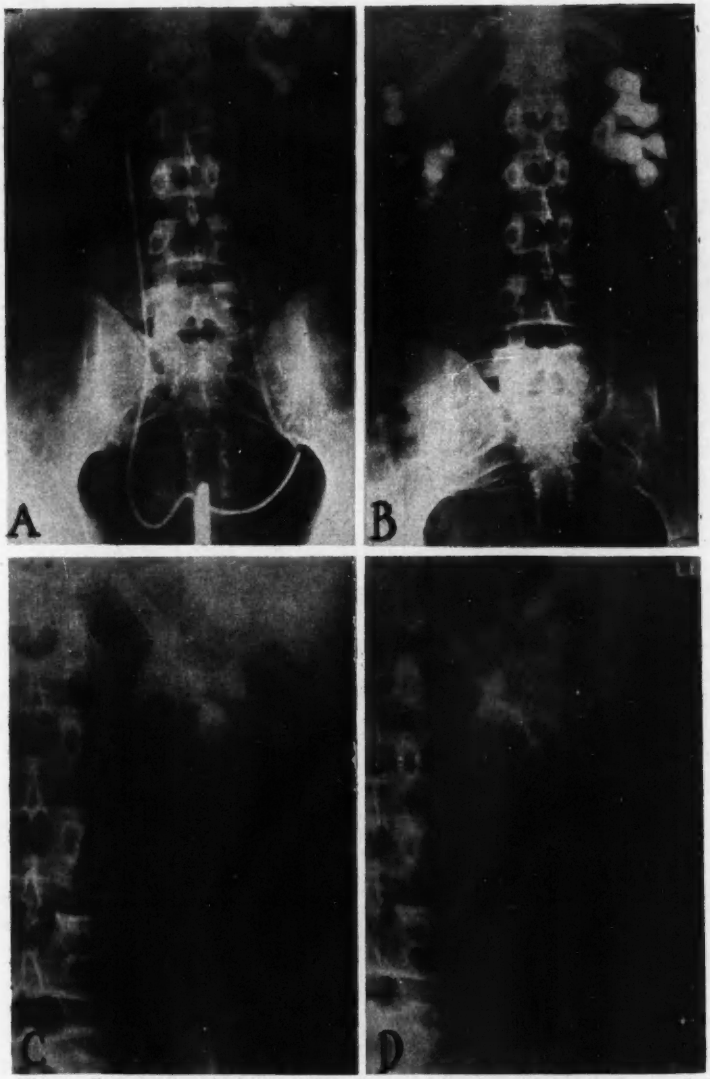


Fig. 4. Case A. B. *(A)* Right kidney is pyonephrotic, with many stones. Left kidney shows hydronephrosis, upper third of ureter very narrow. *(B)* Film just before withdrawing T-tube. Hydronephrosis unchanged, ureter patent. *(C)* Intravenous urogram six months after intubated ureterotomy. Hydronephrosis still present, upper ureter widely open. Right kidney has been removed. *(D)* Intravenous urogram three and one-half years after ureterotomy. Pelvis returned to normal size. Patient in perfect health, urine sterile, renal function normal.

45 per cent in thirty minutes. A No. 14 Braasch bulb was passed to the left kidney with ease, encountering no resistance whatever at any point.

The patient has remained perfectly well ever since, a period of four years and three months. About six months ago another uro-

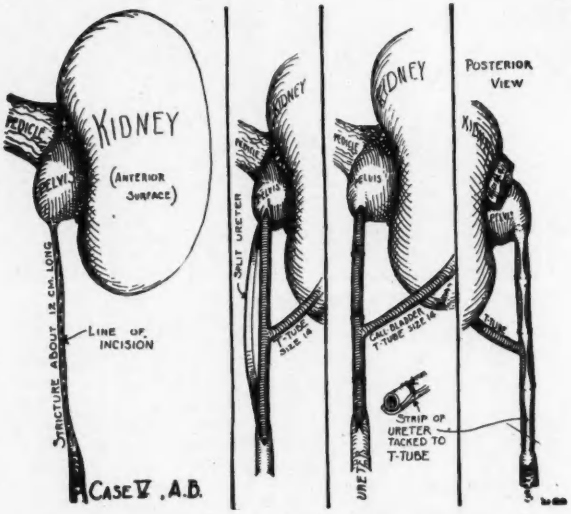


Fig. 5. Case A. B. Stenotic part of ureter incised for its entire length, T-tube inserted, ureteral ribbon held in contact with T-tube by a few sutures of fine plain catgut.

gram was made, more than three and one-half years after operation (Fig. 4, *D*). The hydronephrotic pelvis has shrunk until its outlines can, I believe, properly be called normal particularly for a solitary kidney. The ureteropelvic junction and ureter also appear normal.

Just how ureters perform their function after intubated ureterotomy is still an unanswered question. With the ending of the war it has now been possible to renew experimental studies in an effort to answer this question, and to show what happens to the uretral musculature after healing takes place. The results of these studies will be reported as soon as they are completed.

255 S. 17th St., Philadelphia, Pa.

URETERAL INJURIES

LEON HERMAN, M.D., LLOYD B. GREENE, M.D., AND BENJAMIN L. HAYLLAR, M.D.

Philadelphia, Pennsylvania

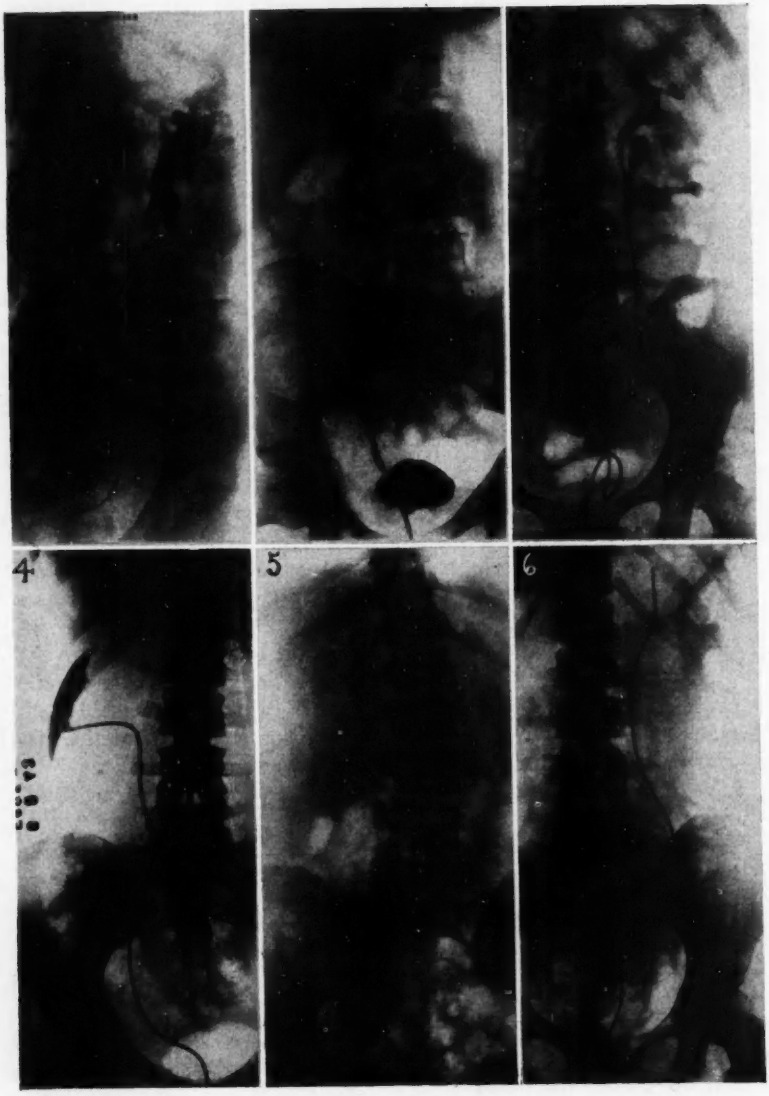
We have reviewed, fairly completely, the literature on the subject of ureteral injury, for the past ten years. There was a total of fifty-eight papers, which lead us to believe that the subject has been very well covered and that ureteral injury is a common occurrence. Our only excuse in making this presentation is to report our experience in the diagnosis and management of sixteen patients suffering from ureteral injury from a variety of causes.

Ureteral injuries may be classified under three general headings, on the basis of the causative factor: (1) external violence; (2) spontaneous rupture; and (3) instrumental injuries and surgical trauma.

Ureteral injury from external violence is very unusual in civilian practice, but serious injuries may result from pelvic fractures. Even in military surgery there are comparatively few reported instances of ureteral injury. Kimbrough could find but eight such cases among a group of 235 patients suffering from urological war injuries. Fromstein and Epstein could report but four injuries to the ureter from the Russian Army. It is entirely possible and quite probable that there were many ureteral injuries associated with other such serious wounds that they caused the death of the victims on the battle field and consequently were never tabulated. We have not encountered an injury of the ureter from external violence.

Spontaneous rupture of the normal ureter is extremely rare. We found one case, in our review, reported by Smith. We report the following case.

Case 1.—Spontaneous rupture of the left ureter or pelvis. R. W., a white man, aged fifty years, was admitted to the hospital on May 18, 1944 complaining of pain in the left loin, which appeared ten days before admission without obvious cause. The initial examination failed to disclose any signs of urinary disease or injury. The next day the abdomen was slightly distended, and tenderness and rigidity were noted in the left renal area.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A No. 5 ureteral catheter introduced to the level of the left kidney drained clear urine in a continuous flow until 8 or more ounces were removed. The urine was sterile and free from blood and pus. Prompt elimination of phthalein in full concentration served to rule out advanced hydronephrosis. The symptoms were relieved by drainage and reproduced by injection of contrast medium. The medium was widely distributed outside the kidney; the pelvis was not shown (Fig. 1, *1*).

On May 23 approximately 500 c.c. clear, blood free, sterile urine was evacuated by loin incision from the left perirenal space. On June 1 purulent urine containing B. proteus was removed by catheter from the left kidney, and the catheter was left indwelling for several days. One year later the urine and renal function were normal, but there were unmistakable signs of prostatic carcinoma with bone metastasis, of which there was no evidence one year before.

Comment. Evacuation by catheter of a large quantity of clear urine from the perirenal space and functional normality of the kidney seem to preclude catheter perforation of a hydronephrotic sac. Furthermore, the formation of a large perirenal collection of clear urine eliminates the possibility of renal rupture. In the case described, it seems justifiable to conclude that the catheter entered the perirenal space by way of a rent in the ureter or pelvis.

Spontaneous rupture of the diseased ureter, usually at the site of an impacted calculus, is not unusual. Figure 1, *2* illustrates the spontaneous rupture of the abdominal segment of the ureter at the site of two previous ureterolithotomies in a patient with an acquired single kidney infected with B. coli. Recovery followed incision and drainage, but a large pseudo-diverticulum formed at the site of the abscess. Permanent nephrostomy was done four years ago and the patient has done very well since.

Spontaneous rupture of the abdominal segment of the ureter also occurred at the site of previous ureterolithotomy when a stone became impacted below this point, in a man aged sixty (Fig. 1, *3*). Urinary fistula persisted after incision and drainage of the abscess, until a practically functionless and badly infected kidney was removed.

Instrumental perforation or rupture of the normal ureter is most unusual since this structure is highly resistant to perforation by the ureteral catheter. Mild contusions and lacerations are common enough and the sequelae are well known to every practicing urologist. While stricture may conceivably result from such trauma, the probabilities

Fig. 1. (Opposite page) *(1)* Spontaneous rupture of left ureter or pelvis with periureteral extravasation of contrast medium. *(2)* Spontaneous rupture of ureter at site of two previous ureterolithotomies in patient with acquired single kidney. *(3)* Postoperative pyelogram. *(4)* Catheter perforation of kidney with injection of opaque medium under true capsule. *(5)* Periureteral extravasation following use of loop catheter in attempt to extract ureteral stone. *(6)* Catheter perforation of lower segment of severed ureter. In attempt to introduce catheter into bladder by way of distal ureteral segment, instrument perforated ureteral wall and was passed downward behind bladder.

are that little permanent damage results. During the past few years, we have from necessity used catheters, in our routine work, that we consider potentially dangerous, and minor trauma has resulted much more frequently than when we had the good pre-war catheters. It was with one of these stiff catheters that we perforated the renal cortex dislocating its capsule (Fig. 1, *4*). The contrast medium, injected through the catheter, is shown between the capsule and kidney substance. The patient, a young woman, suffered only slight and temporary discomfort from the accident, which was followed some forty hours later, by pyelolithotomy and nephropexy from which she recovered uneventfully.

Perforation of the diseased ureter by the ureteral catheter may occur. It most often happens at the site of an impacted stone, but may occur in any pathological situation in which friability of the ureteral structure results.

Periureteral abscesses often occur spontaneously at the site of long impacted stones, but not always as the result of actual perforation with urinary extra-vasation, in fact the kidney may be functionless. This is illustrated in the case of a woman, eighty, in which the catheter deflected by a stone had perforated the ureter to enter a preformed abscess cavity. Recovery followed incision and drainage of the abscess; there was no urinary leakage.

Catheter perforation of the ureter, even if followed by periureteral injection of skiodan may cause no inconvenience.

A sixty-two year old man had a persistent fistula following suprapubic prostatectomy on admission to our clinic. Two operative attempts to close this had failed. The vesical outlet was normal. The right kidney was normal, the left one functionless. The left ureter was obstructed at 1.5 cm. The urine was purulent and paracolon bacillus was cultured therefrom. Suspecting an infected hydronephrosis of a pelvic kidney we injected 10 c.c. skiodan which surrounded the ureter. No harm resulted and on November 29, 1935, a normally placed pyonephrotic kidney was removed. The bladder fistula closed promptly.

At the last meeting of the Mid-Atlantic Section, one of us showed a loop catheter and reported on its employment in extracting small calculi from the distal 6 cm. of the ureter. We then believed that this was an almost harmless device for this purpose but we have since had reason to change our opinion and now regard it as potentially dangerous. It must be said in extenuation that when Dr. Balkus, the designer of the catheter, was working with us and he made the catheters, we had no trouble. It is possible that our efforts in making them have been clumsy. At any rate, they may have a sharp projection from the tip, when the loop is made, that can cut like a knife. The possibility and probability also exist that

the sharp edge of a stone when caught in the loop within the narrow confines of the ureter might cut through the structure when traction is made on the catheter.

We have had two ureteral ruptures produced by the use of this device.

Periureteral abscess due to catheter perforation. D. P., a white woman, aged fifty, was admitted to the Bryn Mawr Hospital on June 22, 1944, with a small stone in the right pelvic ureter which could not be dislodged by catheters. On July 5 a loop catheter was used without success, and mild reaction followed. However, the ureter was patulous but on July 7 ureterograms showed extravasation (Fig. 1, *5*). At operation a T tube was placed in the ureter proximal to the perforation. The stone was not found. Recovery was uneventful and restudy on November 17 disclosed a stone-free, practically normal upper urinary tract.

A forty-one year old man was first admitted with ureteral colic in 1938 and from then until January, 1945, he passed many small stones, with instrumental assistance, on twelve occasions. At that time laboratory studies indicated for the first time the possibility of hyperparathyroid disease; a parathyroid adenoma was found on exploration by Dr. Walkling. A fairly large stone was then present in the abdominal segment of the right ureter and a small stone in the lowermost calyx of the left kidney.

In June, 1945, the calculus from the left kidney was in the pelvic segment of the ureter and an attempt was made to extract it with the loop catheter. The attempt failed and periureteral extravasation resulted. This was drained through a Gibson incision and the stone recovered.

The larger stone was removed from the abdominal segment of the ureter, in October, 1945. The serum phosphorus was 3.3 mg. per cent and the calcium 9.9 mg. per cent. He was then in good health and free of stones.

Serious injury to the ureter commonly results from the employment of rigid instruments, spirals, stone baskets, et cetera. Rusche and Bacon reported fifteen cases of serious injury with two fatalities following intraureteral instrumentation, six of which resulted from the use of spirals or baskets. Wishard, Councill, Cabot and others have, likewise, reported instances of ureteral rupture from the use of these instruments. That there are many unreported cases is attested by the fact that Dourmashkin has knowledge of twenty such cases "scattered about the country." In some of these situations one of the wires was broken and perforated the ureter; in others the ureter was cut or ruptured. Here again one wonders about the possible damage that might result from the sharp edge of a stone

when traction is made. In spite of the often dramatic effect that one might produce by delivering, to the patient, his stone, at the end of a cystoscopic procedure, we are still inclined to the opinion that rigid instruments had best not be employed in intraureteral manipulations.

Fatal peritonitis following rupture of the left ureter. A male student, aged nineteen, consulted a urologist, to whom we are indebted for this case history, in February, 1937, because of left renal colic. On February 16, 1937, a urogram failed to visualize the left kidney; the right one was normal. No stone was found but a No. 6 catheter was momentarily arrested at 3 cm. within the left ureter. Retrograde pyelography disclosed dilatation of the left ureter and pelvis. A No. 8 bulb catheter and a Howard "stone-dislodger" were used. The urine was sterile.

After leaving the hospital, bougies (10-11) and the stone dislodger were used on two accasions, as an office procedure, the last time on March 27, 1937. Five days after this when brought to the hospital, the patient was found to have generalized peritonitis. Much purulent fluid was evacuated from the peritoneal cavity and the abdomen closed. Drains were placed at the supposed site of the ureteral injury through a lateral extraperitoneal incision.

One of us saw the patient on April 5 and again on April 7 when it was decided to reopen the abdomen, but death occurred immediately after anesthesia was induced.

Surgical injuries to the ureter occur more frequently in gynecological operations than in other surgical procedures because of the anatomical relationship of the ureter to the pelvic organs of the female and the difficulty involved in the dissection, in complicated cases. That portion of the ureter which passes through the broad ligament is the most vulnerable. Adams in 1943 reviewed the literature and found a total of 782 reported instances of ureteral injuries during the course of gynecological surgical operations. He added three cases. From his review he concluded that the accident occurs rarely, in the experience of a single operator.

In the woman's clinic at the Pennsylvania Hospital during the period from 1936 to 1945 there were four injuries to the ureter, from a total of 7,966 gynecological operations. There was no injury to the ureter recognized during the same period in a series of 15,325 deliveries which includes 1,568 Caesarian sections. Wood reported the rupture of a ureter in a woman during the course of a normal delivery. The accident was unrecognized and was discovered at autopsy twenty-four hours after delivery.

Injury to the ureter may go unrecognized and, especially, if it be ligation of one ureter. However, uretero-vaginal fistula may result as in the following two cases from an unsuspected injury. The following are typical examples of uretero-vaginal fistula; we have treated six cases.

Uretero-vaginal fistula following hysterectomy. A. S., a white woman, aged thirty-two, had a hysterectomy in another city. Nine days later a vaginal fistula developed. The local urologist attempted repair of the injury but could not mobilize the ureter. The patient was admitted to the Pennsylvania Hospital on May 25, 1945. Examination disclosed right ureteral obstruction at 2 cm. and the catheter passed through the fistulous tract into the vagina. The urogram showed moderate dilatation of the right upper urinary tract.

The kidney on the injured side retained good function and was apparently uninfected. However, the urograms suggested obliteration of a considerable segment of the pelvic ureter. This, together with the fact that an unsuccessful attempt at repair had been made, seemed to justify nephrectomy, which was done successfully.

A. P., a white woman, aged thirty-three, had a hysterectomy on October 13, 1944, in another hospital. Eight days after operation "there was a sudden gush of water from the vagina." On admission to the urological ward at Pennsylvania Hospital examination was negative except for foul watery discharge from the vagina and a tear in the vaginal vault. The bladder was intact. The urogram showed delayed function on the right side with the pelvis visualized in seventy-five minutes and the right ureter to a point just below the pelvic brim in 105 minutes. The left kidney was normal.

The right ureter was obstructed at 9 cm. Indigo carmine appeared in full concentration from the left ureteral orifice in three minutes; none from the right ureteral orifice or from the fistulous tract in twenty minutes.

We did a nephrectomy in this case because the high position of the ureteral injury and advanced renal damage seemed to preclude successful conservative surgery.

The following four cases are from the woman's clinic of the Pennslyvania Hospital. They were operated upon by four different surgeons. They are examples of complete division of the ureter, three accidentally and one intentionally, in which immediate repair was made over an ureteral catheter.

Clamping with division of the right ureter during hysterectomy; end to end anastomosis. B. G., a white woman, aged forty-two was subjected to hysterectomy on January 29, 1941, during the course of which the right ureter was clamped and cut 2 cm. from the bladder. A catheter introduced by cystoscopy was arrested at 2 cm. An ureteral catheter was then passed from above into the bladder and to the renal level and the severed ends of the ureter joined over the catheter with

three interrupted sutures of No. 000 chromic catgut. A small rubber-covered drain was placed near the site of the injury. Cystoscopic extraction of the bladder end of the catheter through the urethra completed the operation.

A small urinary fistula developed in the abdominal incision. On the fifteenth day, the No. 5 catheter in the ureter was replaced by a No. 6 catheter because of pain in the right flank and rise in temperature. After this the wound healed rapidly. The patient was discharged February 17. Eight months later the kidney was found to be normal in function, not dilated, and the urine free of pus.

C. M., single, colored woman, aged thirty-one, was admitted on September 27, 1943. An enormous fibroid uterus together with a large tubo-ovarian abscess were removed on October 25. The elongated left ureter which coursed over a portion of the mass was accidentally severed. After removal of the uterus, the ends of the severed ureter were mobilized and the distal end of a No. 5 catheter passed to the kidney, but the proximal end, after passing through the lower segment of the ureter, met obstruction. This end of the catheter was then withdrawn and a portion cut away. The shortened catheter was then reinserted presumably into the bladder via the ureter. The ureteral ends were then united with several interrupted sutures of No. 5.0 chromic catgut.

Cystoscopic examination failed to disclose the end of the catheter in the bladder.

As shown by x-ray studies it lay behind the bladder, having perforated the ureter at or near the uretero-vesical junction (Fig. 1, *6*). Vaginal examination was negative.

The patient was transferred to our service on October 29. We exposed the dilated ureter surrounded by edematous tissue through a loin incision. The ureter was opened, the catheter removed, and a 20 F. soft rubber catheter passed to the kidney level and fixed in position by skin sutures. The bladder was drained by an indwelling catheter. The urine contained nonhemolytic streptococci.

On November 4 the excretion of phthalein from the right kidney was 35 per cent; the left, 20 per cent. Pyelograms made by injecting medium through the drainage tube showed moderate dilatation of the pelvis.

On November 8 the catheters were removed, and on the following day cystoscopy was performed, the left ureter catheterized, and the catheter left indwelling. A Foley catheter was placed in the bladder.

Transient signs of intestinal obstruction were relieved by intubation and on November 15 the catheters were removed. The loin fistula healed promptly and on November 23 the patient was discharged in fine condition.

C. T., a single white woman aged thirty-seven, was admitted on August 20, 1943, with a fibro-myomatous enlargement of the uterus to about the size of a seven month pregnancy. Supravaginal hysterectomy was done on August 20.

The right ureter, much elongated by stretching over an intraligamentous portion of the tumor, was severed at the level of the uterine artery. After removing the uterus, the ureter was shortened by excising about 4 inches of the proximal segment and the ends joined together over a catheter. The abdomen was closed without drainage. The bladder end of the catheter was brought through the urethra by means of cystoscopic forceps. Fourteen days later the catheter was removed and recovery was uneventful.

V. J., thirty-five year old colored woman, had a hysterectomy for fibroid uterus complicated by division of the right ureter. The injury was repaired by end to end anastomosis over a catheter with satisfactory results.

Three weeks after leaving the hospital, she was admitted to our wards with a tentative diagnosis of subphrenic abscess secondary to cortical abscess of the right kidney. The case proved to be one of acute pyelonephritis which responded to catheter drainage, sulfonamide therapy and blood transfusions.

Eleven days after admission, pyelography disclosed moderate dilatation and reduction in function of the right kidney. The patient was dismissed on July 10, clinically well and with clear urine.

End-to-end anastomosis over an ureteral catheter was employed in each of the above cases. The final result in each case was satisfactory. If it had been recognized that the catheter was not in the bladder, in the second case before the ureter was sutured in might have been withdrawn and inserted through a cystoscope, thus saving the patient the hazard of a second operation. There is no excuse for failure to drain the site of the anastomosis. It should always be done. This patient was operated upon again four days after the primary anastomosis. Ureterostomy seemed to us to be the procedure of choice; a T tube might have been better. It has been suggested by McIver, and others that the anastomosis of the ureter be made over a T tube and judging from D. M. Davis' use of it in ureteral surgery, it should be ideal. It is probably best to insert the tube above the site of the point of anastomosis of the ureter. Careful observation by a competent urologist is certainly desirable, in these cases. Obstruction and infection must be anticipated and recognized promptly when and if they occur. Nephrostomy and ureterostomy as secondary procedures must be done when indicated.

Ureteral injuries occurring during urological and abdominal operations. The ureter may be severed during resection of the bladder or diverticulectomy. The injury is usually treated by ligation or reimplantation of the ureter into the bladder. Reimplantation

seemed to prolong the life of the one of our patients whose opposite kidney was destroyed later by calculus pyonephrosis.

Surgical injuries of the upper ureter occur in difficult renal surgery. Thus, in one of our cases while mobilizing a fistulous, single kidney containing stones, the ureter was torn from the pelvis. The patient was alive and self-supporting seven years after closure of the plevis, removal of the stones and permanent nephrostomy. The normal ureter may rupture if put under tension as happened during simple pyelolithotomy in the practice of a colleague. The undiscovered accident was followed by urinary fistula and renal infection necessitating nephrectomy.

Division of one ureter, usually the left, may occur during resection of the large bowel and may go undiscovered until complications arise as in the following case.

Uretero-cutaneous fistula following intestinal resection. D. B. C., a man aged thirty-seven, had a Mikulicz resection of the descending colon for carcinoma in 1941. Recurrence necessitated removal of the sigmoid colon and rectum in March, 1944, following which a urinary fistula developed at the site of the colostomy wound. The left ureter was obstructed at 2 cm. An extensively diseased kidney was removed May 19. Recovery was uneventful.

Our experience with conservative surgery in the treatment of such cases has been unsatisfactory, and in the absence of real necessity of conserving renal tissue, nephrectomy is the procedure of choice.

Medical Arts Bldg., Philadelphia, Pa.

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CYTOLOGY OF THE URINE SEDIMENT IN NEOPLASMS OF THE URINARY TRACT

GEORGE N. PAPANICOLAOU, M.D.

New York City, New York

I consider it a privilege and an honor to have the opportunity to present a paper at this meeting of so many distinguished and outstanding urologists, and I want to express my deep appreciation to Dr. Alexander R. Stevens for the invitation which he has extended to me. Dr. Stevens, as the head of the Department of Urology, has helped us more than any one else to carry out our studies by giving us his wholehearted support and extending to us the facilities of his Department. We are most grateful to him for his valuable co-operation.

It is only a little more than a year and half since Dr. Stevens, Dr. Marshall and I had our first conference and decided to proceed with the exploration of the possibility of diagnosing malignant neoplasms of the urinary tract by smears prepared from urine sediment. I must confess that at that time I was rather pessimistic as to the outlook of this project. I thought that the rapid cellular disintegration which occurs in the urine would make it difficult to obtain exfoliated cells in a good state of preservation, permitting an accurate cytologic evaluation.

In order to prevent or retard the cellular disintegration of the exfoliated cells, we mixed the urine, as soon as it was obtained, with 95 per cent alcohol and then centrifuged it without delay. Smears were prepared from the sediment and fixed promptly in a solution of equal parts of 95 per cent alcohol and ether. Through this immediate fixation, we succeeded in obtaining a good preservation of the structural details of the exfoliated cellular elements.

The smears were handled further and stained with the technique developed for the diagnosis of uterine cancer by the vaginal smear.[8] This method was described in detail in a monograph published in 1943 by Dr. Herbert F. Traut and me.[10] Since then, it has been in-

The work reported here was conducted in the Departments of Anatomy and Urology of Cornell University Medical College and the New York Hospital in co-operation with Dr. Victor F. Marshall and was aided by the Commonwealth Fund. The material was obtained chiefly from the New York Hospital and the Memorial Hospital of New York.

troduced in several hospitals in the United States as well as in Canada, Mexico and South America. It is also used in some public health laboratories and in cancer detection clinics, as a screening method for singling out early carcinomas of the uterus.

The smear technique should not be considered as a substitute for biopsy, curettage or any other standard method of diagnosis, but as an adjunct to them. Its greatest virtue is that it permits recognition of malignant neoplasms at a relatively early stage and in instances in which other diagnostic methods may fail. This point has been fairly conclusively proven by us and other investigators.[1-7] During our routine smear examination at the Woman's Clinic of the New York Hospital we have repeatedly diagnosed unsuspected cases of carcinomas of the uterus, as well as a number of carcinomas in situ. The latter are often asymptomatic and cannot always be recognized by other diagnostic methods.

The early appearance of exfoliated cancer cells in the vaginal and other secretions is evidently due to the high proliferative activity of these cells, which results in an increased superficial exfoliation. Thus, one may find exfoliated cancer cells in a relatively early developmental stage of a malignant neoplasm.

The technique applied in urine sediment smears and the results obtained during the early part of our investigation were reported about a year ago in a preliminary note by Dr. Marshall and me.[9] The statistical evaluation of our results at that time was based on only eighty-three cases. Since then, we have studied over 500 cases. Lately, we have adopted a new method of classification of our reports, but our technique has remained unchanged. The present status of our investigation will be illustrated by a number of tables and photographs.

TABLE 1. TECHNICAL PROCEDURE FOR URINE SEDIMENT SMEARS

1. Mix urine as soon as possible with 95% alcohol, a minimum of 1 part alcohol to 2 parts urine.
2. Keep in refrigerator until centrifuged.
3. Centrifuge without much delay for 10 to 15 minutes.
4. Pour off supernatant fluid. Prepare smears from sediment.
5. Coat clean slides with film of albumen. Spread sediment evenly.
6. Wait until edge of smear shows beginning dryness, then immerse slides in mixture of 95% alcohol and ether, equal parts.
7. Fix smears in alcohol-ether for 20 minutes or longer. Avoid drying. Smears may be kept in alcohol-ether indefinitely, until ready to stain.
8. Stain with method described in Science, 95:438, 1942.

TABLE II. CLASSIFICATION OF REPORTS ON URINE SEDIMENT SMEARS AS APPLIED TO THE DIAGNOSIS OF MALIGNANT NEOPLASMS OF THE URINARY TRACT

Class I.	Absence of abnormal or atypical cells.
Class II.	Atypical cells present but without abnormal features.
Class III.	Cells with abnormal features but not sufficiently pathognomonic.
Class IV.	Fair number of pathognomonic cells and cell clusters.
Class V.	Large number of conclusive cells and cell clusters.

Table I describes the technique used in urine sediment smears which is practically similar to that used in vaginal smears.

Table II shows the classification which we now use for our smear reports. Findings are often of inconclusive character, and it would be rather misleading to classify them as either positive or negative. The present classification is more flexible and permits a more accurate formulation of the reports. From the point of view of a more general statistical survey, Classes I and II may be considered as negative, III as suspicious, and IV and V as positive.

Table III shows a tabulation of 240 recent cases in which the smear reports have been classified according to Table II. The percentage of errors in the negative group (Classes I and II) is 7.36 per cent, in that of the positive group (Classes IV and V) 3.45 per cent. It is to be noted that the two false positives in Classes IV and V were both papillomas. In the intermediate group (Class III) 47.37 per cent were finally diagnosed as positive, 5.26 per cent re-

TABLE III. ACCURACY OF REPORTS ON URINE SEDIMENT SMEARS FOR THE DIAGNOSIS OF MALIGNANT NEOPLASMS OF THE URINARY TRACT

	Class	I	II	III	IV	V
	Total number of reports 240	96	67	19	13	45
		163		19	58	
Final Diagnosis	Positive 76 Pathologically: 68 Clinically: 8	5 (5.20%)	7 (10.45%)	9 (47.37%)	12 (92.3%)	43 (95.56%)
		12 (7.36%)			55 (94.83%)	
	Doubtful 4	1 (1.04%)	1 (1.49%)	1 (5.26%)	0	1 (2.22%)
		2 (1.22%)			1 (1.72%)	
	Negative 160	90 (93.75%)	59 (88.06%)	9 (47.37%)	1 (7.7%)	1 (2.22%)
		149 (91.42%)			2 (3.45%)	

TABLE IV. ANALYSIS OF CASES INCLUDED IN TABLE III.

Class	I	II	III	IV	V
Positive:					
Bladder	3	4	6	8	34
Kidney	1	2	2	2	5
Prostate	1	1	1	2	3
Pelvis	0	0	0	0	1
Negative:					
Papillomas	6	14	1	1	1
Hypertrophy of prostate	21	21	2	0	0
Cysts of kidney	4	1	1	0	0
Hematuria	4	2	0	0	0
Pyelonephritis	1	0	0	0	0
Prostatitis	1	2	1	0	0
Cystitis	5	2	0	0	0
Miscellaneous	48	17	4	0	0

mained doubtful and 47.37 per cent have been diagnosed as negative.

Table IV shows the relative distribution of the positive cases according to the organs involved; also some of the pathological conditions which prevailed in the negative group. The miscellaneous group includes a good many carcinomas of other organs outside of the urinary tract.

Some cases have been diagnosed primarily or exclusively by urine sediment smears. Among these, two may be mentioned, one referred by Dr. Howard S. Jeck (No. 121) and another by Dr. Allister M. McLellan (No. 296). In both, the provisional diagnosis was hypertrophy of the prostate without any clinical symptoms suggestive of malignancy. The smears were positive and in both instances a malignant neoplasm was found to be present in a diverticulum of the bladder. Although these tumors were relatively small and concealed, the exfoliation was rather prolific, as shown by the large number of abnormal cells present in the smears.

Among the early cases, I may mention that of a papilloma with early malignant changes (No. 200). This was diagnosed as such by urine sediment smears primarily. Papillomas may be often identified through the exfoliation of certain distinctive cell types (Fig. 1, *4*).

Case 342 was originally diagnosed by smears as a carcinoma of the bladder. Cystoscopy, and three bladder biopsies performed at the time the urine specimen was obtained, were all negative for a neoplasm and a diagnosis of cystitis was made. A second biopsy

performed eleven days later, proved the existence of a carcinoma of the bladder.

Most of the specimens sent to our laboratory have been of voided urine. We also had a number of catheterized specimens, which appear to be more dependable as they usually contain more numerous and better preserved cells. The number of ureteral specimens

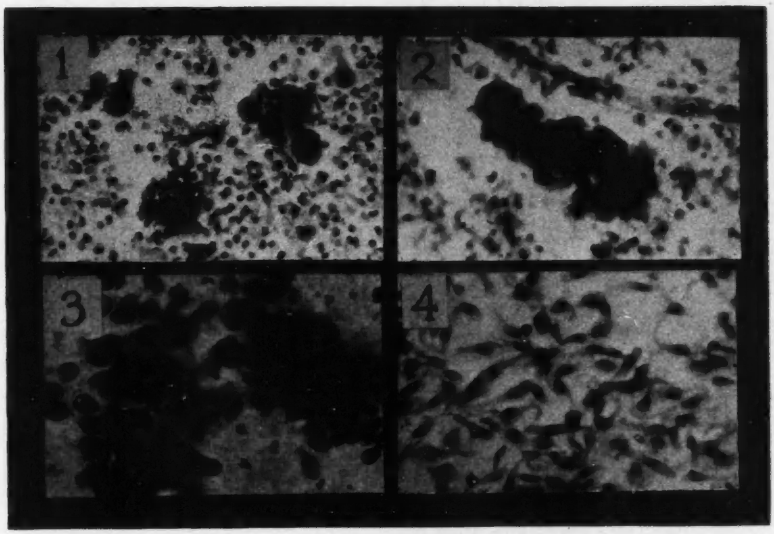

Fig. 1. Photomicrographs of urine sediment smears. *(1)* Carcinoma of the kidney. *(2)* Carcinoma of the prostate. *(3)* Carcinoma of the bladder. *(4)* Papilloma of the bladder. × 285.

examined has been relatively small. Their cytology presents certain specific characteristics which require special study.

A conclusive positive diagnosis should be based as much as possible on clusters of malignant cells or small fragments of cancerous tissue and not on single exfoliated cells. The criteria, therefore, are not exclusively cytologic (structural abnormalities of the nucleus and of the cytoplasm), but also histologic (anisocytosis, anisonucleosis, crowding of the cells, irregular pattern, etc.).

Figure 1 shows clusters of malignant cells in a carcinoma of the kidney *(1)*, a carcinoma of the prostate *(2)*, and a carcinoma of the

bladder *(3)*. Figure 1, *4* shows elongated and columnar cells from a benign papilloma of the bladder.

The exfoliated normal cells, as a rule, have fairly uniform and inactive nuclei in contrast to the active and more variable and aberrant nuclei of the carcinoma cells. Despite the marked histologic differences evidenced in sections of carcinomas of various types and organs, the cytologic modifications and abnormalities of the different forms of exfoliated cancer cells found in smears show a fairly uniform pattern. This greatly facilitates the identification of malignant neoplastic cells in the smear, but, at the same time, it makes more difficult the recognition of their distinctive type and of their origin. From this standpoint, the smear test appears to be at a disadvantage, which, however, is partly offset by the fact that it covers a much larger area than the biopsy.

On the basis of the results obtained so far, we believe that the application of the smear test in urological cancer diagnosis can be commended as a morphologically sound and dependable laboratory procedure which complements and corroborates other means of diagnosis, and also helps in recognizing early or hidden malignant lesions.

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DISCUSSION

DR. LEON HERMAN (Philadelphia, Pa.): What part do mitotic figures play in the diagnosis?

DR. GEORGE N. PAPANICOLAOU (New York, New York): Mitotic divisions are found rather infrequently in exfoliated cells. Since most of these cells are fairly degenerated, the mitotic figures are usually poorly preserved and cannot be easily identified. The largest number of mitoses which I have observed was in an endometrial smear of a sarcoma of the uterus.

DR. HOWARD JECK (New York, N. Y.): I wish to express my appreciation of Dr. Papanicolaou's presentation. Last year I had a male patient in the New York Hospital who was something of a puzzle. Dr. Papanicolaou helped very materially in solving it.

This patient, sixty-seven years old, was a Syrian who had adopted Haiti as his residence and place of business. He spoke only Arabic and French of the Haitian variety—a difficult type of French to understand. The fact that I could not converse freely with him was in large measure responsible for my inability to arrive at a satisfactory diagnosis sooner than I did. Since he was very fearful of being hurt, he resented greatly most instrumental efforts to examine him.

His chief complaint was marked dysuria, day and night.

By rectal digital palpation this patient had a typical adenomatous hyperplasia of the prostate gland. It was about four times the normal size of the prostate. He had varying amounts of residual urine —from two ounces to a pint or more. The urine was grossly cloudy, at times bloody and exceedingly foul smelling.

Cystoscopy ws not very satisfactory. After a fleeting glimpse of the bladder neck was obtained, which seemed to substantiate the diagnosis of hypertrophied prostate, the patient complained so bitterly that the cystoscope had to be removed at once.

Intravenous urograms revealed a right kidney pelvis which appeared to be normal and a slightly distended left kidney pelvis and left ureter. Since the bladder outline did not show up at all well, cystograms subsequently made in the usual manner indicated a normal bladder outline.

In the hope of improving the condition of his urine, suprapubic

drainage was performed. A digital examination of his bladder at this time revealed nothing striking.

The very foul urine with its large pus content and at times blood, suggested two other diagnostic possibilities, namely, a diverticulum and the presence of cancer. A specimen of the urine was given to Dr. Papanicolaou. He very promptly reported the presence of cancer cells. A second cystogram afforded no additional information. A day or two later, a second specimen of urine was given to Dr. Papanicolau. He stuck to his guns and again promptly reported cancer cells. Secretion from the prostate gland was then sent to Dr. Papanicolaou. No cancer cells were found.

A third cystogram was made and this time great care was taken to drain all the contrast medium from the bladder after the first film was exposed. The second film revealed a diverticulum about 5 cm. in diameter apparently situated posterior to the bladder and slightly to the left side of the midline.

Under spinal anesthesia, the patient was again cystoscoped. Dr. Stevens was present at this examination. We found no evidence of cancer in the bladder but just back of the trigone and somewhat to the left of the midline was a diverticular opening. The cystoscope could not be introduced into this opening. No evidence of growth about the opening was seen.

But the absence of cancer in the bladder plus the presence of cancer cells in the urine, plus the knowledge that he had a diverticulum of the bladder enabled us to make the correct guess, namely, cancer within the diverticulum.

At the time of the prostatectomy, which soon followed, this was proven. Before removing the prostate, the diverticulum was explored by introducing the index finger. Friable tissue was felt and a piece removed. A frozen section, made immediately, disclosed cancer.

A Syrian surgeon (a friend as well as a physician of the patient) was present at the operation. He objected so strenuously to removal of the diverticulum and its contents that the patient still has his cancer.

The prostatectomy presented no difficulties and the patient made an uneventful recovery.

DR. FLETCHER H. COLBY (Boston, Mass): I think this is too good to pass by lightly. Dr. Papanicolaou's contribution is ex-

tremely important, and we are very fortunate to have heard him describe this perfectly beautiful piece of work. I have talked recently with Dr. Fremont-Smith and Dr. Meigs at the Massachusetts General about this. It seems to represent a great advance in the early diagnosis of cervical cancer. They have done, I think, between two and three thousand vaginal smears, with the correct diagnosis being made over 95 per cent of the time. Dr. Meigs recently told me that in their experience this method had been more accurate in certain instances of cervical cancer than biopsy, particularly in early cases.

This method then represents an advance in gynecology, and I believe that it perfectly well can represent an advance in our early diagnosis of cancer of the urinary tract.

Biopsy with us has not always been reliable, and here is another method which may well help to make an early diagnosis of cancer.

During the past week a patient at the hospital was suspected of having a papillary carcinoma of the renal pelvis. As is frequently the case, the diagnosis was not clear cut. The urinary sediment was sent to the laboratory, and a diagnosis of carcinoma, unqualified, came back. The patient was operated upon and did have a papillary carcinoma of the renal pelvis.

It seems to me that one place where this might be of use is in scrotal conditions where hydrocele fluid is present and you suspect that there may be a malignant tumor of the testis. Have you had any experience with that, Dr. Papanicolaou?

DR. PAPANICOLAOU: We have had no occasion to examine fluid from a hydrocele, but we have had several specimens of fluid from various types of cystic growths. In a recent case of a tumor of the thoracic wall, smears prepared from aspirated fluid contained malignant cells which were reported. A subsequent removal of the tumor proved the existence of a malignant neurolemomma.

DR. HERMAN: Have you had any results from bloody exudates in the pleura sac?

DR. PAPANICOLAOU: Yes, we have had about seventy cases of pleural and peritoneal fluid. The technique which we use in these fluids is the same as in the urine. A rather disturbing element in these specimens is the frequent presence of numerous histiocytes which are often difficult to distinguish from cancer cells.

THE COURSE OF HYPERTENSION AFTER NEPHRECTOMY FOR ADVANCED UNILATERAL RENAL DISEASE

NELSON W. BARKER, M.D., and WILLIAM F. BRAASCH, M.D.

From the Division of Medicine and the Section on Urology, respectively, Mayo Clinic, Rochester, Minnesota

It is now more than eight years since Butler[3] reported successful treatment of hypertension in two children by nephrectomy for advanced unilateral pyelonephritis, and since Walters and one of us (Barker)[1] reported a similar result after removal of a kidney seriously damaged by chronic atrophic pyelonephritis in an adult. Since that time there have been a number of reports of the incidence of unilateral renal disease among patients who had hypertension and the results of removal of the affected kidney. It is apparent that excellent results have followed nephrectomy in some cases, and that there has been no effect on the hypertension in others.

For a patient whose primary complaints or symptoms are definitely related to an advanced "surgical" lesion of one kidney and who has incidental hypertension, the immediate therapeutic problem is simple, since nephrectomy probably would be necessary and advisable whether or not hypertension was present.

However, in the treatment of a patient whose presenting problem is hypertensive disease and who does not have symptoms or physical signs suggestive of localized renal disease, the internist and urologist are confronted with two questions. First, should a urographic examination be made? Second, if it is made and if local or diffuse disease of one kidney is found, should the patient be subjected to nephrectomy primarily as treatment for the hypertension?

The incidence of so-called surgical renal lesions in cases of hypertension was at first considered to be high, some observers stating that it occurred in approximately 40 per cent of cases. It soon became apparent, however, that in some cases of hypertension minor lesions of the kidney were found which were coincidental and not etiologic factors. This group included such renal lesions as ptosis, pyelectasis of slight or moderate degree, urinary infection and renal

lithiasis, without significant renal destruction. It has also become apparent that significant lowering of blood pressure rarely has followed nephrectomy unless the kidney was badly diseased as the result of either chronic infection, such as occurs in the presence of atrophic pyelonephritis and severe hydronephrosis or extensive chronic renal tuberculosis. Even when such advanced lesions of the kidney have been found in patients who have hypertension, the effect on the blood pressure of removal of the involved kidney has been rather variable.

There are many factors involved in determining the exact incidence of surgical renal lesions associated with hypertension, and the incidence is difficult if not impossible to determine. A previous review[2] of a large series of cases of hypertension, in which careful urologic studies were made at the Mayo Clinic, showed that renal lesions amenable to surgical treatment occurred in less than 1 per cent of patients who had hypertension. In reviewing our cases of hypertension with renal lesions, this approximate incidence would seem to be corroborated.

In the sifting out of renal lesions in cases of hypertension, the most valuable single method of diagnosis is the excretory urogram. The urogram usually will make visible the existence of a renal lesion which may be surgical. Generally, other data will be required to complete the diagnosis. No diagnostic method is available which will offer specific data as to whether or not hypertension would be eliminated if the kidney were removed. The question has been raised as to whether an excretory urogram should be made routinely in every case of hypertension. It has been our practice to make excretory urograms for hypertensive patients who (1) give a history of disease of the urinary tract, (2) have microscopic hematuria or pyuria, or other manifestations suggesting disease of the urinary tract, or (3) are less than twenty years of age, if no other cause for hypertension is apparent, such as coarctation of the aorta. We have made excretory urograms for a great many other patients with hypertension who could not have been included in the above groups, but not for all, and it is possible that in a few cases, hypertension of renal etiology was overlooked. We have felt that excretory urograms are not of value for patients with hypertension who are more than sixty years of age or for those who have definite azotemia.

One of the most difficult problems in cases of hypertension has

been to determine whether a renal lesion detected in the course of clinical examination of a patient with hypertension could be on etiologic factor or was merely coincidental. All the clinical data in such cases have been carefully weighed in the decision as to the advisability of surgical treatment. In many cases the hypertension was known to have existed for many years, and the possibility of renal etiology seemed minimal. In other cases the renal lesion was of such a minor type that it was very evidently coincidental, and could not possibly have been an etiologic factor. In a few selected cases, although the renal lesion seemed to be a questionable etiologic factor, surgical treatment was advised. Where there was a very definite renal lesion which might well be an etiologic factor, operation was, of course, always advised. In the course of routine examination many instances of advanced hypertension wtih definite surgical lesions of the kidney were observed, but because of the patient's general condition, or because of clinical evidence of bilateral renal disease, performance of renal surgery was not advisable.

POSTOPERATIVE COURSE OF HYPERTENSION AFTER RENAL SURGERY

This report is based on a review of sixty-one cases. All the patients came to the Mayo Clinic primarily because of hypertension. All were found to have advanced disease of one kidney and minimal, if any, evidence of disease in the other kidney. All underwent removal of the diseased kidney. There were no deaths in the hospital during the postoperative convalescence. Blood pressures were checked several times from two to four weeks after nephrectomy to determine the immediate effects of nephrectomy on the hypertension. Blood pressures were checked again two to four years after nephrectomy, either during a subsequent examination of the patient at the clinic or by the patient's home physician. Thirty-two patients, or slightly more than half of the total number, were examined five or more years after nephrectomy. The remainder either could not be traced or insufficient time had elapsed since nephrectomy in which to permit a five-year follow-up study. Results have been graded as follows: *Good*—if blood pressures, expressed in millimeters of mercury, were 150 systolic and 100 diastolic, or less; *Fair*—if blood pressures were significantly reduced, but still were above 150 systolic and 100 diastolic; *Poor*—if there was no significant effect on the blood pressure; and *Death*—if patients died during the period of

the follow-up study. The results for the entire group are given in Table I.

In reviewing the results of operation it is interesting to note the comparative condition of the patient at different periods after the operation. When the blood pressure was taken within two to four weeks after operation, it was found that the result was either good

TABLE I. POSTOPERATIVE RESULTS: SIXTY-ONE HYPERTENSIVE PATIENTS WHO UNDERWENT UNILATERAL NEPHRECTOMY

Result	Time After Operation		
	Immediately (2 to 4 Weeks)	Two Years Plus	Five Years Plus*
Good	31	25	10
Fair	13	10	5
Poor	17	20	11
Death	0	6	6
Total	61	61	32

* Figures in this column based on 32 traced patients.

or fair in forty-four cases, or 72 per cent. However, when these patients were examined two years after operation, there were only thirty-five patients for whom the results were good or fair, or 57 per cent. Five years after operation the number of patients whose condition was described as good or fair was only fifteen, or 47 per cent of the thirty-two who were followed for that period (Table I).

Attention has been called previously to the fact that an estimate of results of renal surgery for hypertension cannot be exact unless the patients are examined as late as two years after operation. It was thought that if the patient's condition is satisfactory at that time, the chances are that the benefit will be permanent. However, the reduction in the percentage of good results at the end of five years in comparison with the percentage of good results two years after operation shows that this assumption was fallacious. In other words, even though elimination of the kidney has a very definite effect in lowering blood pressure immediately after the operation and as long as two years after operation, other factors may arise to cause a return of hypertension. The comparatively temporary removal of the etiologic factor in hypertension by renal surgery was not fully appreciated. That factors remain which may reassert themselves after the immediate benefit of renal surgery has elapsed

must be admitted. Nevertheless, the fact that the blood pressure of fifteen patients was approximately normal five years after operation demonstrates conclusively that the diseased kidney which was removed was a definite etiologic factor in the hypertension. It is also evident that elimination of the etiologic factor of hypertension, as accomplished by nephrectomy, was in many cases of only temporary value and that an underlying factor existed which reasserted itself to permit a return of the hypertension.

Careful review of the twenty-six cases in which the results of operation were classified as "poor" or "death" revealed data which were of considerable interest. It was rather noticeable that in most cases in which there was evidence of some involvement of the opposite kidney, there was little or no reduction in hypertension after nephrectomy. Cicatricial deformity as shown in the urogram or in the outline of the "good" kidney is observed in many of these cases. In several cases there was less than normal function in the "good" kidney, as shown by the results of various clinical tests of renal function. Elevation of blood urea, even though moderate, retardation of the secretion of phthalein, or deficiency in clearance of urea, should constitute a warning against removal of one kidney as treatment for hypertension alone, unless there is renal pathologic change which urgently indicates nephrectomy. In fact, several patients with clinical or urographic evidence of disease in the "good" kidney were observed whose general condition became worse after nephrectomy. Roentgenograms showed minute areas of calcification or small stones in both kidneys in several cases. The well kidney had been subjected to previous operation for stone in two cases.

The group of cases in which there was a definite reduction in blood pressure, but not a return to normal, is interesting. In many of these the systolic blood pressure observed before nephrectomy was more than 200 mm. of mercury, and the diastolic, 120. Five years later, although the blood pressure was reduced, it remained between 160 and 170 systolic, and between 90 and 100 diastolic. Associated with the reduction in blood pressure there was almost invariably an improvement in the patient's general condition and well-being. In the absence of any other form of treatment, it would be logical to assume that removal of the kidney was the differential factor. It would seem very probable that the reduction in blood pressure was caused by elimination of a pressor factor which had

been present in the removed kidney. In several cases of severe hypertension, the blood pressure decreased almost to normal for a variable period after nephrectomy, but when the patient was observed two to five years later, a moderate increase in blood pressure was noted, but at a much lower level than before the operation.

In a number of cases in which the results were classified as

TABLE II. POSTOPERATIVE RESULTS: TWENTY-NINE PATIENTS WHO HAD RENAL ATROPHY AND FIBROSIS AMONG SIXTY-ONE HYPERTENSIVE PATIENTS WHO UNDERWENT UNILATERAL NEPHRECTOMY

Results	Time After Operation		
	Immediately (2 to 4 Weeks)	Two Years Plus	Five Years Plus*
Good	12	10	4
Fair	5	5	3
Poor	12	11	5
Death	0	3	3
Total	29	29	15

*Figures in this column based on 15 traced patients.

"poor," the hypertension remained at approximately the same level after nephrectomy, but the patient's general condition was very definitely improved. Some type of renal infection had been present in most of these cases, and it is evident that removal of this infection was the cause of improvement in the patient's general condition. From the standpoint of the hypertensive disease, it is probable that both the fair results and temporarily good or fair results of only two years' duration can be considered of sufficient benefit to the patient to justify nephrectomy. Even a partial lowering of the blood pressure, or a temporary lowering of blood pressure for a period of two years, prevents part of the inevitable strain on the cardiovascular system produced by the hypertension, and thus delays the inevitable breakdown of the heart or large vessels.

The group of sixty-one cases can be broken down into three groups according to the nature of the disease in the kidney which was removed. In twenty-nine cases there was marked renal atrophy and fibrosis (Table II). In each of these cases the kidney which was removed weighed less than 115 gm., and in twenty-one of the twenty-nine cases it weighed less than 70 gm. In most of these

cases the lesion was considered to be chronic atrophic pyelonephritis. In a few it was probably congenital hypoplasia with secondary pyelonephritis. In twenty-six cases there was advanced hydronephrosis with evidence of previous or active infection and with considerable destruction of the renal parenchyma by cicatrization (Table III). The function of these kidneys was markedly im-

TABLE III. POSTOPERATIVE RESULTS: TWENTY-SIX PATIENTS WHO HAD HYDRONEPHROSIS AMONG SIXTY-ONE HYPERTENSIVE PATIENTS WHO UNDERWENT UNILATERAL NEPHRECTOMY

Result	Time After Nephrectomy		
	Immediately (2 to 4 Weeks)	Two Years Plus	Five Years Plus*
Good	14	12	5
Fair	7	4	2
Poor	5	7	5
Death	0	3	3
Total	26	26	15

*Figures in this column based on 15 traced patients.

TABLE IV. POSTOPERATIVE RESULTS: SIX PATIENTS WHO HAD RENAL TUBERCULOSIS AMONG SIXTY-ONE HYPERTENSIVE PATIENTS WHO UNDERWENT UNILATERAL NEPHRECTOMY

Result	Time After Operation		
	Immediately (2 to 4 Weeks)	Two Years Plus	Five Years Plus*
Good	5	3	1
Fair	1	1	0
Poor	0	2	1
Death	0	0	0
Total	6	6	2

*Figures in this column based on 2 traced patients

paired. In the other six cases there was advanced tuberculosis with destruction of more than 50 per cent of the renal parenchyma; sometimes with almost complete destruction of the renal parenchyma (Table IV).

The results in the three groups of cases are given in Tables II, III and IV. No definite difference in the results was noted in the three separate groups.

Of the entire sixty-one patients, twenty-five were male and thirty-

six were female. There were almost four times as many female as male patients in the group with chronic atrophic pyelonephritis, and there were a few more males than females in the group with hydronephrosis. Of the entire group 64 per cent of the males and 53.7 per cent of the females still had good or fair results after two years.

TABLE V. RESULTS TWO YEARS AFTER NEPHRECTOMY AMONG SIXTY-ONE HYPERTENSIVE PATIENTS, ACCORDING TO PREOPERATIVE LABILITY OF BLOOD PRESSURE

Blood Pressure, Status	Results	
	Good or Fair	Poor or Death
Relatively labile	18	11
Relatively fixed	17	15

We have been impressed by the fact that both good and poor results have followed nephrectomy for patients who had very similar renal lesions. From the standpoint of the hypertensive disease itself, careful study of the data in this group of cases failed to yield information which would lead to a prediction as to which patients might be expected to obtain good and which poor results after removal of the badly diseased kidney. In this series of sixty-one cases the known duration of the hypertension, the known duration of the renal disease, the results of urinalysis and the electrocardiographic observations failed to give information which would aid in the prediction of good or poor results after nephrectomy. Studies of the relative lability or fixation of the blood pressure, including the cold pressor test, studies of the blood pressure after the patient had rested in bed for a period of twenty-four hours and after he or she had received barbiturates, also failed to show differences which might aid in the prediction of results (Table V).

The patients were divided into four groups on the basis of retinal examination, according to the Keith-Wagener classification, namely: Group I—those who did not have sclerosis of the retinal arteries or retinitis; Group II—those who had sclerosis of the retinal arteries but no retinitis; Group III—those who had sclerosis of the retinal arteries and retinitis, but without edema of the optic disks; and Group IV—those who had sclerosis of the retinal arteries,

retinitis and edema of the optic disks. Results which followed nephrectomy in these various groups are shown in Table VI. There were both good and poor results in all groups, but relatively more good results were obtained in Group II. There was no significant variation in results obtained among individuals in various age groups, although results were slightly better for individuals less

TABLE VI. RESULTS OF NEPHRECTOMY AS SHOWN BY RETINAL EXAMINATION TWO YEARS AFTER OPERATION: SIXTY-ONE HYPERTENSIVE PATIENTS WHO UNDERWENT UNILATERAL NEPHRECTOMY

Keith-Wagener Classification*	Results	
	Good or Fair	Poor or Death
Group I	6	4
Group II	20	9
Group III	5	8
Group IV	4	5

* See text for explanation of this classification.

than twenty years of age and for those between the inclusive ages of thirty and thirty-nine years.

It is obvious that since hypertension usually occurs in the absence of severe unilateral renal disease and that severe unilateral renal disease not infrequently is found in patients who do not have hypertension, the combination of the two conditions at times may be entirely coincidental, possibly in as many as 20 to 30 per cent of cases in which both conditions are found. Even if unilateral renal disease may have been the cause of the hypertension, it would seem that in a given case sooner or later irreversible vascular changes may take place diffusely in the body and in the good kidney, which would prevent relief of the hypertension, even if the original cause is removed. These two possibilities may explain the poor results which followed nephrectomy in cases in which all observations seemed to be similar to those made in other cases in which good results were obtained.

In review of the pathologic data, evidence of infection, either active or dormant, was noted in the tissues of all kidneys removed. In all cases of hydronephrosis, extensive pyelectasis also was present. It has been shown, both experimentally and on the basis of clinical records, that unilateral retention of urine with back pressure such as occurs with hydronephrosis, in itself would not be a cause

of hypertension. It would seem, therefore, that the changes in the renal tissue as a result of infection probably are the important factors which favor the intrarenal secretion of pressor substances. So far, no one has been able to determine the exact histologic changes which cause secretion of pressor substances. Of the various hypotheses suggested as the cause of pressor secretion, intrarenal circulatory imbalance (Page and his co-workers[4]) would seem to be most plausible. The microscopic appearance of the tissues in two atrophic pyelonephritic kidneys which have been removed for hypertension may be very similar, and the hypertension may persist in one case and it may disappear in the other. There are no specific clinical, urographic or pathologic data which would give definite preoperative indication as to the possibility of eliminating hypertension if the kidney is removed.

SUMMARY

An analysis has been made of sixty-one cases of hypertension in which advanced unilateral renal disease was found and the affected kidney was removed as treatment for the hypertension.

Follow-up studies in this group of cases have shown that two years after nephrectomy results were good in twenty-five cases, or 41 per cent; fair in ten, or 16.4 per cent; poor in twenty, or 33 per cent, and that six patients, or 10 per cent, were dead.

The condition of thirty-two patients was followed for five years. At the end of this time good results were present in ten cases, or 31 per cent; fair results in five, or 15.6 per cent; poor results in eleven, or 34.4 per cent; and six patients, or 19 per cent, were dead.

Both good and poor results were noted among patients in different age groups, in both sexes and among patients who had various degrees of severity of hypertensive disease. Clinical analysis of these cases from the standpoint of the hypertension failed to reveal information which was of value in preoperative prediction of the effect of nephrectomy on the subsequent course of the hypertension.

No specific urologic or pathologic observations were noted in the affected kidneys which would indicate whether good or poor results would follow nephrectomy.

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HYPERTENSION DUE TO UNILATERAL RENAL DISEASE

ARTHUR H. CROSBIE, M.D., AND JOSEPH FISCHMANN, M.D.

From the Department of Surgery of the Tufts Medical School, Boston, Mass., and the Urological Department of the Cambridge Hospital, Cambridge, Mass.

Although it is generally accepted that the diseased kidney plays an important rôle in the pathogenesis of hypertension, the problem as to its extent is still in the realm of research work. Consequently the question for the clinician is whether elimination of the suspected kidney could be the proper treatment to cure hypertension. In the long chain of etiologic factors participating in development of hypertension, the kidney, by all means, constitutes an outstanding item. Since Goldblatt's fascinating results in producing and curing experimental hypertension are known, clinicians have been trying laboriously to apply them to the benefit of human hypertension with much disappointment and only sporadic real success.

There cannot be any doubt, that among those so-called "essential hypertension" cases there are but a few the etiology of which definitely shows the diseased kidney as the primary origin of the ailment. Consequently there are but a few cases known which have been treated successfully by surgical removal of the diseased kidney.

Experimental results of Goldblatt et al., Houssay, Cruz Coke. Braun-Menendez, Croxatto H., Croxatto R., Tigerstedt, et cetera, obviously proved that the diseased (ischemic) kidney produces a chemical substance, which has a vigorous pressor effect on the blood pressure. This humoral etiological principle of certain cases of renal hypertension can now be considered as reliably proved. In our opinion true humoral renal hypertension is only one type of the essential hypertension group; there is, *ceteris paribus,* another much larger group, the etiology of which originates from disturbances in the nerve mechanism of kidney function. This has been proved by many sympathectomized cases of Smithwick. We incline to state that the number of "neurogenous hypertension" cases overwhelmingly exceeds that of those based on humoral etiology.

These considerations obviously show the difficulties in selection of the cases submittable to nephrectomy. It is extremely hard to tell what type or degree of kidney impairment is sufficient to cause ischemia, which in turn would result in renal hypertension. There are no simple rules. Another difficulty is to tell whether the other kidney, although not showing detectable changes, is intact, or at least intact enough to be deprived from the still considerable excretory activity of the kidney to be removed. Our investigative methods cannot tell yet whether removal of one kidney will decrease satisfactorily the blood pressure when the other may already be damaged to a certain extent.

The most common condition in which unilateral kidney disease with hypertension occurs is hyperplastic sclerosis of the kidney vessels. Chronic pyelonephritis is very apt to cause this type of pathological change; however the tubular apparatus has to be kept functioning sufficiently in order to supply renin (angiotonin, hypertensin, et cetera). Stone disease may cause the necessary changes in the kidney to be followed by hypertension in one patient but not in another. Braasch, Walters, and Hammer have shown that perinephric abscess, malignancy, and tuberculosis are not responsible for hypertension. Chronic infection causes hypertension only if the simultaneous sclerotic blood vessel changes are advanced enough.

The most obvious group of renal hypertension is that which comprises conditions where there is a lesion directly affecting the blood supply to the kidney by diminishing the caliber of the main artery. To this group belong tumors exerting pressure on the artery or parenchyma, thrombosis, aneurysms, arteriosclerotic plaques, congenital hypoplasia of the artery, et cetera.

The degree of impairment of the excretory function of the kidney has no deciding value in establishing indication for nephrectomy for there is no parallelism between function and hypertension. It is a rather rare occurrence, as it was in our case, that complete lack of function exists thus simplifying the indication for nephrectomy.

The following case has been considered by us as typical "essential hypertension" caused by unilateral kidney disease.

A forty-eight year old woman was taken suddenly sick the first week of October, 1944. She had never been seriously ill previously. After having taken a long hike, she complained of headache. However, the

next day she drove her automobile over one hundred miles. One week later she complained of severe pain in the right neck and shoulder region, and was unable to lie flat in bed because of breathlessness. A few days later dimness of vision in both eyes was noticed so that she was unable to read. The ophthalmologist found retinal hemorrhages in both fundi. On admission to the Wesson Hospital in Springfield, Massachusetts, October 30, 1944, her main complaints were severe dyspnea with inability to sleep, dizziness, headache, and impaired vision so that she could not see at all. Blood pressure at that time was 180/140. The urine showed a specific gravity of 1.017 to 1.028, albumin varying between plus or minus to 2 plus. One specimen showed 1 to 3 red blood cells, nonprotein nitrogen 40 mg. per cent. A chest film showed some free fluid in the right pleural cavity. Cardiac treatment consisting of digitalis and ammonium chloride was instituted. She gradually recovered from the dyspnea and orthopnea although the blood pressure continued to range from 140/110 to 180/130. Once every three to four days she would vomit without apparent cause. The Fishberg concentration test showed 12.5 per cent excretion in fifteen minutes, 2.5 per cent in thirty minutes, and 5 per cent at the end of sixty minutes, making a total of 20 per cent. After about two or three weeks the patient was discharged from that hospital fairly well recovered as to her general condition except the impaired vision. The diagnosis was essential hypertension, glomerular nephritis with cardiac decompensation and retinal hemorrhages.

On December 26, 1944, the patient was admitted to the Cambridge Hospital with persisting eye trouble and blood pressure of 158/118. The urine showed 5 to 6 white blood cells and 2 to 3 red blood cells, and a very slight trace of albumin. The nonprotein nitrogen was 32 mg. per cent. The patient had no urinary symptoms. Ophthalmological examination revealed old and fresh retinal hemorrhages in both eyes, more on the right than on the left. There was extensive exudation in both eyes.

Intravenous pyelography revealed good function of the left normal kidney with no function of the right kidney at all. The right kidney also appeared to be small. A right retrograde pyelogram showed a small kidney with normal calyces; no flow of urine through the catheter (Fig. 1).

Dealing with a completely functionless kidney, we performed nephrectomy on January 5, 1945.

Following the operation the blood pressure immediately dropped to 110/80 and was maintained at that level till the patient got up first, when the pressure went up from 130/80 to 140/100. This pressure was maintained up to the time of the first postoperative follow-up examination on February 1, 1945. At the next follow-up examination on April 4, 1945 the blood pressure was 135/75.

During her stay in the hospital, immediately after the operation, the patient reported daily of steady improvement of her vision so that from

the sixth postoperative day on she has been able to read without any difficulty.

Recent ophthalmological examination revealed very little change in the appearance of the eye grounds. There is scar formation in the right eye involving the fovea, whereas central vision of the left eye has been preserved.

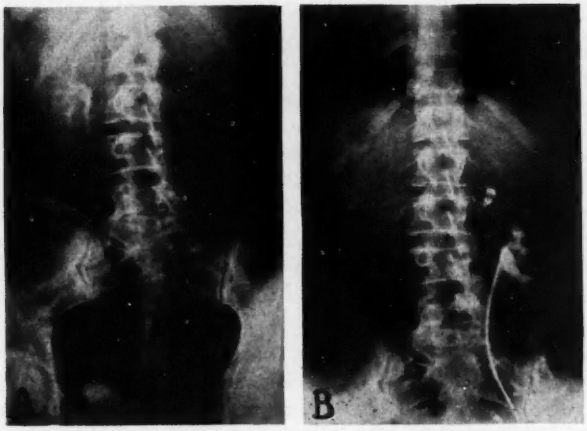

Fig. 1. (*A*) Intravenous urogram, and (*B*) retrograde pyelogram before operation.

At the last follow-up examination the patient had not had any complaints and felt as well "as ever before."

The kidney weighed 57 gm. and measured 8 by 3.5 by 3 cm. The surface was finely granular and showed some scarring. It was of chocolate brown color. On opening the kidney, the cortex appeared narrowed, measuring from 0.3 to 0.5 cm. in width. There was fairly good demarcation between the cortex and the medulla. The mucosa of the pelvis and calyces was markedly thickened and showed several petechial hemorrhages on the surface (Fig. 2).

Dr. H. E. MacMahon's microscopic diagnosis was: Diffuse tubular atrophy and intimal sclerosis of the vessels of the kidney. The only explanation for this lesion would appear to be in the nature of an arteriosclerotic narrowing of the main renal artery adjacent to the aorta (Goldblatt type of nephrosclerosis). This would also explain the clinical picture before and after nephrectomy.

In summing up the effect of nephrectomy in this case we believe, as many others do, that it is not only justifiable but even urgently indicated to submit every case of so-called "essential hypertension" to

thorough urological investigation. According to the findings and the duration of the hypertension, the procedure to be followed has to be decided upon.

I saw this patient personally last on September 18, 1945, when she was free of any complaints, except weakness of vision of the right eye whereas she was able to see with the left eye so that she did not

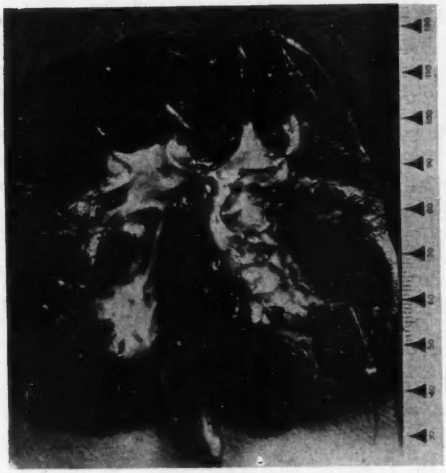

Fig. 2. Kidney removed at operation.

have any visional difficulty. The blood pressure was 130 over 90. She reported having been feeling very well, without any complaints during the time elapsed since the nephrectomy (eight and one-half months earlier). Actually she felt better during this period of time than at any time before as far as she could remember. Thus it seemed as though we had a brilliant cure of hypertension by removal of a Goldblatt kidney. Shortly after this I left for the South to be gone all winter.

On November 2, 1945 she was seen by my associate Dr. Joseph Fischmann, who was called in for consultation. At that time the patient reported having had severe dyspnea during the previous three weeks. The dyspnea started with sudden onset without any known reason. She has been treated by a local physician who found the blood pressure rapidly increasing up to 175/110, and later 200/150. He also noticed a peculiar mental reaction and nervousness with some confusion, getting steadily worse until admission.

On November 7, 1945, the patient was readmitted to the Cambridge

Hospital. Physical examination revealed a pale, anxious-looking woman, sitting on the bed, with her legs drawn up under her. She was dyspneic. Numerous moist râles were present at the bases of both lungs. The heart was enlarged to the left; the sounds were forceful, rapid, and regular; there was a soft murmur, most probably systolic in time, at the apex, transmitted to the axilla; no presystolic murmur was heard; at the base and along the left border of the sternum, there was a soft diastolic murmur; P_2 was increased; there was a questionable systolic murmur in the aortic area; rate 100. Blood pressure on admission was 180/120. There was no tenderness anywhere. Neurological: With pupils dilated by homatropine, vessels were small and seemed sclerotic. The discs were swollen, no optic cup, edges difficult to see. No hemorrhages were seen. No definite changes were noted in the cranial nerves. The extremities moved; all reflexes were very active. No clonus or Babinski. The nonprotein nitrogen on admission was 38, on the twelfth day after admission 66. Urine: Specific gravity, 1.017, rare red blood cell, and white blood cell. On the twelfth day the urine contained a trace of albumin, 15 to 25 white blood cells. Hinton and Wassermann tests were negative. An x-ray of the chest showed circulatory congestion of both lungs, the heart dilated. The patient was given bromides. After digitalization she showed some improvement for one week, then she became progressively worse. She died on the thirteenth day.

Autopsy (Dr. H. E. MacMahon): Most outstanding, and from a urological point of view, a highly interesting feature of the autopsy was a recent thrombosis of the renal artery of the remaining kidney completely occluding the vessel. It extended into both of the two main branches where it gradually dwindled away. The kidney weighed 130 gm. It measured 10.5 by 4.5 by 3.5 cm. There were a few firm, pale, slightly elevated areas with a dark red outer border. The corticomedullary junction was somewhat indistinct, but evident. Summary of the miscroscopic examination was as follows: (1) Varying degrees of ischemic atrophy (Goldblatt kidney) of right kidney (removed surgically ten months previously to death); (2) recurrent focal proliferative endarteritis involving renal arteries, pulmonary vessels, and aorta, and periarteritis with recent thrombosis of remaining renal artery and infarction of kidney; (3) tuberculosis of lungs and regional lymph nodes, and miliary tuberculosis of the myocardium; (tubercle bacilli demonstrated in sections of lymph nodes); (4) necrotizing lesions in the walls of the arterioles of the cortex of the adrenal, a finding consistent with malignant hypertension.

The final report was:: "This case appears to fall into a group of vascular allergy, in which the vessels of the kidney have been more severely affected than those of any other organ, resulting in hypertension, complicated by thrombosis. The clinical manifestations are determined by the site of the vascular lesion" (thrombosis of renal artery

of the persisting single kidney). Thus death was caused by renal failure.

SUMMARY

A forty-eight-year-old, apparently healthy woman, was suddenly taken sick with symptoms and signs of severe hypertension. She had marked impairment of vision on both eyes. Urological examination revealed a very small right kidney, lacking any degree of function. Nephrectomy resulted in complete cure including return of vision, and decrease of blood pressure to normal. The patient's condition continued normal until 10 months after operation, when very stormy symptoms and signs of acute cardio-renal failure developed. Death occurred 18 days later of uremia.

We believe that this case is worthy of being reported as another disappointing trial of surgical treatment for hypertension caused by renal disease.

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HYPERTENSION: RESULTS OF SPLANCHNICECTOMY IN PATIENTS WITH ABNORMAL PYELOGRAMS

REED M. NESBIT, M.D., AND ROBERT T. PLUMB, M.D.

From the Department of Surgery, University of Michigan, Ann Arbor, Mich.

While reviewing pyelographic data on cases of hypertension, sixteen abnormal pyelograms were found, and these patients subsequently underwent splanchnicectomy. These sixteen cases constitute the basis for the present report.

All patients have been followed for a year or longer, because it is impossible to evaluate the results of sympathectomy in patients who have been operated upon less than a year.

All the patients had supradiaphragmatic removal of thoracic eighth to twelfth ganglia and approximately 20 cm. of the splanchnic nerves. This in contrast to the technique reported by Smithwick in which the entire splanchnic bed is relieved of its sympathetic control by removing the ganglia from thoracic 8 through lumbar 2.

It is difficult to arrange such a small series in any one way to show conclusive statistical results. However, we believe that the trend is definite and that by means of a larger series to be published later, more definite statements will be possible. Hypertension in itself is a disease complex with great individual variations; it is because of this that discussion of a single phase is difficult.

Thirteen patients were females and three males. The average age was thirty-four, with extremes of seven years and fifty-three years.

In six cases, bilateral pyelonephritis was present, in three to a minimal to moderate degree, while the same number had marked cicatrical changes of pyelonephritis. The remaining ten cases had unilateral disease, ranging from calculus associated with pyelonephritis to hydronephrosis. These data are presented in Tables I and II.

All of the fourteen patients who have been followed (two cases unable to get yearly report) had at least a fall of 10 mm. in the diastolic blood pressure. The majority of the cases had diastolic pressure falls greater than 30 mm. of Hg., the extremes being

TABLE I. RESULTS OF SPLANCHNICECTOMY ON PATIENTS WITH MINIMAL TO MODERATE PYELOGRAPHIC ABNORMALITY

Case	Name	Age	Pathology	Preop. B. P.	Check-up at Months		Results
1	P. C. 498295 Female	41	Bilateral pyelonephritis	200/130	150/90	40	Good; asymptomatic
2	I. S. 500782 Female	33	Rt. neg. Lt. atrophic pyelonephritis	216/110	150/100	46	Fiar to good; asymptomatic
3	M. R. 562136 Female	34	Rt. pyelonephritis; early structural changes Lt. neg.	210/145	130/80	54	Good; asymptomatic
4	V. W. 513400 Female	43	Rt. neg. Lt., cicatricial changes; sup. calyx	188/110	160/82	38	Good; asymptomatic
5	B. B. 521645 Male	43	Rt. renal calc. and early pyelonephritis, Lt. negative	240/140	155/100	36	Fair to good; asymptomatic
6	M. K. 527722 Male	44	Bilateral pyelonephritis	220/120	150/90	29	Good; asymptomatic
7	E. H. 534995 Female	41	Rt. neg.; 1 calc. in minor calyx	240/130	unable to follow; army wife		
8	A. C. 520309 Female	36	Bilateral pyelonephritis	230/138	196/120	32	Poor to fair; asymptomatic
9	L. A. 543661 Female	16	Rt. neg. Lt. pyelonephritis	230/145	140/110	21	Fair to good; asymptomatic
10	W. R. 547768 Male	46	Rt. lyperplasia Lt., absent	200/145	140/80	16	Good

74 to 30. Three had reductions of pressure between 16 and 18 mm. Hg. diastolic pressure, and one case with a fall of only 10 mm.

The average fall in the systolic and diastolic pressure for the entire fourteen cases was 63.5/40.7 mm. of Hg.

If the patients are divided similarly to those of Smithwick where Group I shows a lowering of 30 mm. or more diastolic pressure, Group II of 20 to 29 mm., Group II of 10 to 19 mm., we find that 71 per cent fall in Group I, while 98 per cent fall into Groups I and II.

Many have reported that symptomatic relief is the major result afforded by splanchnicectomy. In Group I we find that all of the patients are free from symptoms following sympathectomy. In

Group II, three out of four have had complete relief of symptoms, and one had no improvement.

In contrast to the above grouping, if the cases are divided into those with marked pyelographic abnormalities and those with minimal to moderate changes, ten cases fall into the later grouping, with nine of the cases being followed (Table I). Six of these had

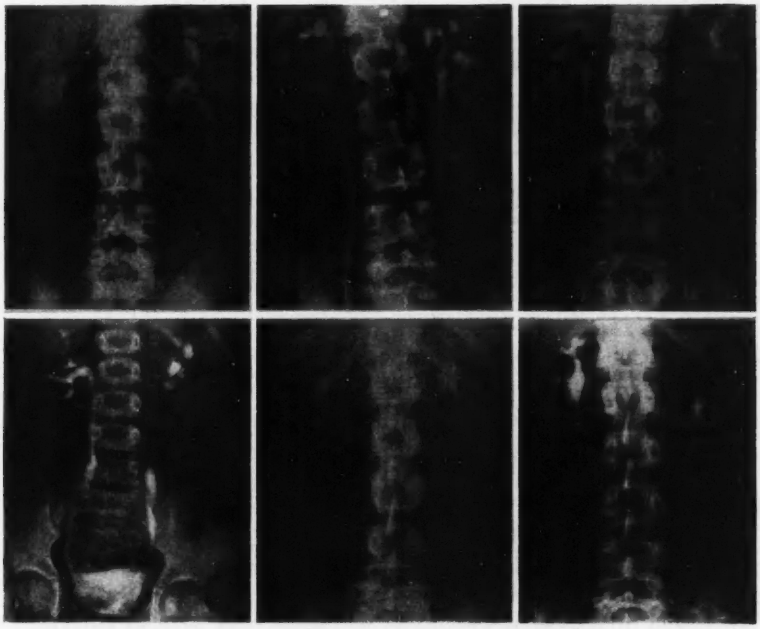

Fig. 1. Pyelograms in six patients who underwent splanchnicectomy. See Table II.

diastolic blood pressure falls greater than 30 mm. of Hg.; two cases with pressure falls of 16-18 mm. Hg. and one with a fall of only 10 mm.

There were six patients with marked pyelographic changes (Table II, Fig. 1). Four had lowering of the blood pressure of more than 30 mm., one had a 16 mm. drop, and one patient who underwent both nephrectomy and splanchnicectomy died two months later of uremia. The four patients with the greatest drop in di-

TABLE II. RESULTS OF SPLANCHNICECTOMY ON PATIENTS WITH MARKED PYELOGRAPHIC ABNORMALITY

Case	Name	Age	Pathology	Preop. B.P.	Check-up at Months		Results
11 (Fig. 1, A)	M. B. 512727 Female	24	Rt. hydronephrosis Lt., neg.	180/140	132/80	39	Good; asymptomatic
12 (Fig. 1, B)	M. S. 559513 Female	53	Bilateral chr. pyelonephritis	288/144	160/94	16	Fair to good; B. P. not quite normal
13 (Fig. 1, C)	G. U. 549206 Female	31	Lt. pyelonephritis Rt. neg.	182/110	140/80	18	Good; asymptomatic
14 (Fig. 1, D)	K. M. 553411 Female	7	Bilateral pyelonephritis	166/126	128/110	16	Fair to poor
15 (Fig. 1, E)	F. B. 533376 Female	20	Rt. early pyelonephritis Lt. atrophic pyelonephritis	210/150	118/60	27	Good
16 (Fig. 1, F)	A. B. 422154 Female	31	Rt. chr. pyelonephritis Lt. neg.	220/132	230/130	9	Failure from nephrectomy
				230/130	180/110	Died 2 mo.	Died of uremia 2 mo. after operation

astolic pressure had complete symptomatic relief, while the one with a drop of only 16 mm. had only moderate relief, of symptoms.

In 98 per cent, regardless of pressure changes, the patients were relieved of hypertensive symptoms. Eight of fourteen cases have had a return of their blood pressure to a normal level.

It is of interest that one of our patients, Case 16, underwent a nephrectomy for right chronic pyelonephritis and a preoperative pressure of 220/130. The urine was negative, nonprotein nitrogen 39.4, and urea clearance of 49-47 per cent. Nine months later the pressure continued at the same level and therefore she was advised to have a splanchnicectomy, following which the pressure fell to 180/110 with symptomatic relief. However, she died of uremia two months later.

CONCLUSION

Splanchnicectomy resulted in symptomatic improvement in most of the patients herein reported, and corresponding lowering of the elevated blood pressures occurred. All of the patients had structural abnormalities of the kidneys that were made evident by

pyelography; some were bilateral and some unilateral, and splanchnicectomy appears to have caused no improvement in one patient whose renal disease was far advanced because she died two months later of uremia.

It appears that gross renal disease does not in itself prevent an effective response to splanchnicectomy, but the operation should not be advocated when the prognosis for life is adversely affected by advanced kidney disease.

DISCUSSION

DR J. DELLINGER BARNEY (Boston, Mass.): I just want to say one word. These papers on hypertension supposedly due to unilateral or bilateral renal diseases have been extremely illuminating, but I think that every paper on this subject and every group of papers should stress more than is stressed the fact that no kidney should be taken out in the presence of hypertension unless there is some good surgical reason for taking it out. I have seen, and I think we have all seen, so many kidneys that were a little bit off, and the surgeon said, "Well, probably that is a factor," and has taken out a pretty good kidney, which in many cases might have been saved. But at any rate, it made no difference at all about the renal hypertension.

There are some factors that we don't understand yet. We can take out a very bad kidney and the pressure may drop for a few months or a year or two, and it will come back just the same. I think that point is important to stress, not so much among ourselves who know a little something about urology, but among general surgeons who don't know so much urology, and among certain other urologists.

DR. REED M. NESBIT (Ann Arbor, Michigan): I would like to discuss Dr. Braasch's interesting paper. In reviewing forty-nine cases of hypertension that we are reporting at the A.M.A., we had, after a lapse of two years, an identical percentage of improvement of good and fair results and an identical percentage of poor results as those reported by Dr. Braasch this morning.

USEFUL CYSTOSCOPIC OPERATING FORCEPS

C. D. CREEVY, M.D.

From the Urological Division of the Department of Surgery, the Medical School, Minneapolis

The cystoscopic forceps which are generally available possess a number of disadvantages. Those which permit good vision (A.C.M.I. forceps with flexible shank, McCarthy forceps for the resectoscope) have jaws too small and fragile for anything more than taking a specimen for biopsy. Those with large and stronger jaws must be used blindly (Braasch, Bumpus), or have so small a channel for irrigating fluid (Lowsley, Young) that any appreciable bleeding so obscures vision as to render the instruments useless for many purposes.

The two forceps described below were designed to overcome these disadvantages, and have proved very useful. The first model was made for use with the McCarthy panendoscope, and was so successful that a second one was made for the resectoscope. They are being marketed by V. Mueller of Chicago.

The first forceps (Fig. 1, *1*) is built into the bridge of the standard panendoscope, and fits both the No. 24 and the 28 sheaths. It consists of the small jaws, *A*, from a Bumpus forceps (supplied by V. Mueller) threaded onto a stainless steel wire, *B*, which passes through a stainless steel tube, *C*, placed in the catheter guide. The tube is fitted with a ring, *D*, for the thumb. Rotation of the wire, handles, and jaws is prevented by a short length of stainless steel tube, *E*, so attached to the first one that it rides the shaft of the telescope. The wire, *B*, terminates in a headless brass machine screw, *F*, which fits into a threaded hole in a downward extension, *G*, of the grip for the telescope. It can be fixed in the desired position by a set screw, *H*. This allows adjustment of the jaws so that when they are opened, one is just visible on each side of the field of the 68-A foroblique telescope. The jaws are opened by pulling the thumb ring back, and closed by pushing it forward.

This instrument has been used with satisfaction in taking specimens for biopsy, in removing small calculi (including fragments

left after litholapaxy), in extracting foreign bodies, and is especially useful in the removal of papillomata. Small ones can be removed with a single accurate bite. The operator can grasp a tumor of medium size by the pedicle and pull it off; it is necessary to remove large tumors piecemeal, but in so doing, one does not damage the wall of the bladder as he may with the resectoscope, and so

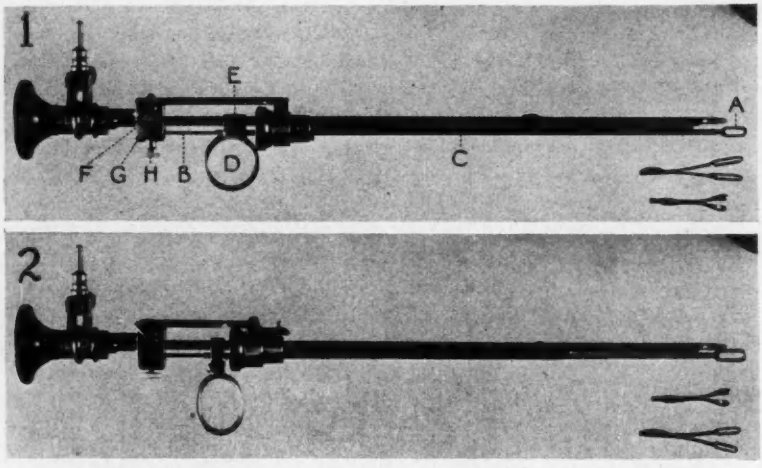

Fig. 1. (*1*) Forceps for panendoscope. (*2*) Forceps for resectoscope.

can get an accurate idea of the size of the pedicle, which can be removed separately for microscopic examination. The bleeding which occurs interferes but little with vision because the instrument has a large channel for irrigating fluid, and is readily controlled by electrocoagulation. Since the forceps have grasping rather than cutting jaws, it is difficult to remove a piece from a hard, infiltrating tumor. For this reason the cutting jaws were taken from a Braasch forceps made by Sklar, and modified so that they are interchangeable with the Bumpus jaws, thus making the instrument considerably more useful. The two types of jaws can be interchanged in a few moments.

The second model was made primarily to meet a special situation which sometimes occurs during transurethral prostatic resection. Occasionally one undercuts a piece of prostatic tissue which proves

to be too large for aspiration through the sheath with an evacuator. Cutting up such a floating piece with the loop is very time consuming, and the McCarthy forceps do not grip the piece firmly enough to permit one to extract it; because of their small size one usually succeeds merely in tearing off a small fragment from the main chunk. Another forceps (Fig. 1, *2*) was therefore constructed, similar to the first, but utilizing the large jaws of the Bumpus forceps, and a modification of the short bridge intended for "converting" the sheath of the Stern-McCarthy resectoscope into a panendoscope. This model has been fitted with a detachable handle. With it, a large chunk of prostatic tissue can be located easily and grasped firmly enough to permit its extraction in one piece, and the instrument is well worth while if used for this purpose alone. The cutting jaws are also usable with this model which can, of course, be used for all of the purposes for which the smaller one is intended. The model shown in the illustration is used with a Nesbit type sheath, i.e., one with a short bevel at the vesical end. A longer forceps would be required for the Stern-McCarthy sheath with its long overhang.

These instruments were made for me by Mr. John Phelan and Mr. John Guptill of the Scientific Apparatus Shop of the University of Minnesota; the details were worked out by them.

SUMMARY

Two cystoscopic operating forceps are presented. It seems to the writer that they have a wider field of usefulness than any others hitherto devised because of their relatively large jaws, adequate channel for irrigating fluid, and excellent vision.

TWELVE YEARS' EXPERIENCE WITH THE BRAASCH-BUMPUS RESECTOSCOPE

BEN D. MASSEY, M.D.
Pasadena, California

During the past sixteen years much has been written about the endoscopic approach to the problem of urinary obstruction. The formative years have passed and the transurethral method should share equal importance with the suprapubic and perineal approach. Transurethral resection today re-emphasizes what perineal prostatectomy emphasized years ago. Genito urinary surgery is a definite specialty requiring selective training of the highest order.

Nothing has been written for several years regarding the Braasch-Bumpus resectoscope. The instrument, now regarded by many as having been a capable instrument for removing small amounts of tissue, has been outmoded and superseded by the somewhat more complicated knife resectoscope of Dr. Gershom Thompson.

It occurred to me that it might be of interest to present very briefly the present form of the instrument, the type of patients cared for, the general procedure of handling the average patient with urinary obstruction, and the summation of our work with private patients in the two Pasadena hospitals in the past twelve years with an analysis of the complications and deaths.

When Doctor Bumpus and I established practice in 1934, I shared his firm conviction that the cold knife resectoscope was the safest instrument, gave the patient the best result with the lowest morbidity. The experiences of the past twelve years have strengthened these convictions.

The greatest single improvement in the Braasch-Bumpus resectoscope was the addition of the irrigating knife; this increased the visibility and permitted very rapid removal of tissue. This improved instrument, like its predecessor, incorporates no built-in carrier for the Bugbee electrode. This was considered a slight disadvantage for several years in that it caused an extra maneuver to control bleeding. However, when we began doing prostatectomies, we found that the shrinking capsule takes care of many of the

vessels. The electrode carrier is frequently used for a few minutes (at the end) following removal of each half of the prostate. The ratio of calibre to visibility is greater in this instrument than in the Thompson instrument and the increased visibility, plus less possibility of stricture, far outweighs the value of an electrode carrier incorporated into the instrument.

The one distinct disadvantage of the Braasch-Bumpus resectoscope is that we have been unable to get the instrument standardized and manufactured to the precision necessary for most efficient use.

TYPE OF PATIENT

Pathologists, who have done extensive work throughout the country and in Southern California, are agreed that the Pasadena area is the center of a population of elderly people who have the most extensive degenerative lesions observed as compared with their findings in any other section of the United States. These people have retired from an active life, seem to be enjoying themselves and are wholeheartedly engaged in trying to prolong their years. I bring out this point as it is important in understanding the type of risk we encounter.

Very few of these patients come with advanced uremia. We have observed some with the mildest forms of prostatism over a period of several years before symptoms justify surgical intervention. Many are seen in their first attack of complete retention or with 200 to 300 c.c. infected residual urine and little or no evidence of renal damage. The advantage of only slight renal damage in these patients is over-balanced by their advanced age, extensive cardiovascular disease, hypertension, with history of previous cerebral vascular accidents and actual or threatened occurrences of coronary thrombosis.

Considering that such patients comprise the largest group of surgical risks, all procedures are directed and carried out in a manner calculated to least upset the patient. Preliminary cystoscopic examination is never done on the obviously obstructed patient. Those in acute retention or with chronically infected residual urine are made comfortable by catheterization and the use of sulfonamides. The patient is admitted to the hospital the afternoon prior to the day of operation; he is given sulfonamides and bar-

biturates the night before and the morning of surgery. Morphine is never given because of its depressing effect and danger of inducing nausea and vomiting. Spinal block anesthesia is given with every effort being made to hold the anesthesia at the lowest level that will relax the bladder. Any fluctuation of blood pressure during surgery is combated with saline and glucose and plasma. If routine blood count proves the patient to be anemic, a transfusion of citrated blood is given during the operation. The cutting time of the operation is limited to one hour and at the end of the procedure a 30 c.c. bag catheter is left inlying without tension. A bilateral partial vasectomy is performed following the resection. Complete removal of all adenoma is desirable; however, if this is not feasible, complete removal of one-half the prostate will give a functional result superior to incomplete removal of all lobes.

Upon the patient's return to his room, the catheter is attached to a closed automatic irrigator and he is permitted to sit up in bed. He is allowed a regular diet beginning with the first meal served following his surgery.

The irrigator is removed the first postoperative day, the catheter is connected to a sterile tubing and gallon bottle, the patient is gotten up in a chair. The catheter is removed in forty-eight hours following a resection of the average amount of tissue; it is removed in seventy-two hours in cases where the obstruction is small and the muscular and fibrous elements predominate. As soon as the patient voids satisfactorily for twenty-four hours after removal of the catheter, and is afebrile, he is permitted to leave the hospital.

This study represents the composite experiences of three men: Dr. H. C. Bumpus, Jr., who was an experienced resectionist at the outset and whose experience in the control of hemorrhage enable us (and I say "us" advisedly) to control bleeding which would have increased the complications and mortality statistics; myself, who had done some resections before 1934 and, like many resectionists, believed my ability was above my experience but who realized, as the years passed, each year of endeavor had improved my skill; and the subsequent association of Dr. Earl F. Nation in 1941, an extremely capable resectionist.

For clarity of presentation, the years 1934 through 1945 have been arbitrarily divided into two groups of six years each. This

TABLE I. TRANSURETHRAL RESECTIONS, 1934-1939

Year	Number of Patients Resected	Number of Resections	Primary	Secondary	
				Delayed	Immediate
				Per cent	Per cent
1934	11	11	11	0.0	0.0
1935	44	46	42	0.0	9.0
1936	54	60	52	1.8	12.9
1937	61	78	55	9.8	27.8
1938	52	58	45	11.5	13.4
1939	47	57	42	8.0	23.4
Total	269	310	247	6.3	13.4

division accidently rather roughly divides the groups on the basis of the manner of resection. By 1939 we had adopted the principle that partial removal should be substituted for as complete a removal as we were able to do as time and the condition of the patient would allow. We believe that transurethral resection for the average patient must give a permanency of results equal to that of any other surgical procedure, or its application to the average patient in the youngest age group would not be justified. From the very beginning we adopted the principle that the operation should be applicable to every patient regardless of the size of the gland. When we fell short of the ideal, we felt it was due to personal shortcomings and not the method; proceeding on this basis, the largest glands were attacked. This was accomplished by the use of preliminary suprapubic cystostomy.

The headings of the first two tables are, in general, self-explanatory. Briefly, primary means a new patient undergoing his first resection. You will note after the first year that the number of patients resected is less than the actual number of resections performed. This difference is explained best by realizing that the

TABLE II. TRANSURETHRAL RESECTIONS, 1940-1945

Year	Number of Patients Resected	Number of Resections	Primary	Secondary	
				Delayed	Immediate
				Per cent	Per cent
1940	48	53	41	16.6	8.3
1941	66	75	61	7.5	13.6
1942	81	87	75	8.6	6.1
1943	102	107	95	7.8	3.9
1944	129	134	114	12.4	3.1
1945	121	124	111	9.9	0.8
Total	547	580	497	10.2	4.9

TABLE III. TRANSURETHRAL RESECTIONS, 1934-1945

Year	Number of Patients Resected	Number of Resections	Primary	Secondary	
				Delayed	Immediate
				Per cent	Per cent
1934 through 1939	269	310	247	6.3	13.4
1940 through 1945	547	580	497	10.2	4.9
Total	816	890	744	8.25	9.25

difference in numbers represents patients having more than one resection during the same year or patients of previous years returning for further resection. The term "secondary" is a poor choice of words and denotes any subsequent resection regardless of time interval between or number of resections after the patient's primary resection. The terms "delayed" and "immediate" under the heading of "secondary" denotes the time interval between resections: "immediate secondary" applies to patients having a subsequent resection within three months of their primary one; the term "delayed" covers the period after three months and in most cases, years.

Table III summarizes the two periods. It shows graphically the increased skill acquired, in that immediate secondary resections dropped abruptly after 1940. The increase in the delayed resections is ascribed to three conditions: (1) the large accumulation of patients resected during the first half of this period who returned with mild recurring prostatism; (2) those upon whom, on their return, we were unable to pass a catheter, and cystoscopic examination revealed adhesions between the remaining lobes; (3) our

TABLE IV. ANALYSIS OF SUBSEQUENT RESECTIONS, 1934-1939

Year	Number of Patients Resected	Number of Patients Needing Subsequent Resections, Benign				Number of Patients Needing Subsequent Resections, Carcinoma				Average Interval In Years Between Delayed Resections
		1	2	3	4	1	2	3	4	
1934	11	2			1					
1935	44	4	1							
1936	54	9	3	2			2			2
1937	61	23	5	1		5	1			¾
1938	52	10	3			1				1½
1939	47	11	3				2			2
Total	269	59	15	3	1	6	5	0	0	
Per cent		21.9	5.5	1.1	0.3	2.2	1.8			

TABLE V. ANALYSIS OF SUBSEQUENT RESECTIONS, 1940-1945

Year	Number of Patients Resected	Number of Patients Needing Subsequent Resections, Benign				Number of Patients Needing Subsequent Resections, Carcinoma				Average Interval In Years Between Delayed Resections
		1	2	3	4	1	2	3	4	
1940	48	10	3	1						2¼
1941	66	11	1							3¼
1942	81	14					2			3½
1943	102	7				2				2½
1944	129	3	1			3				3
1945	121	1				2				4
Total	547	46	5	1	0	7	2	0	0	
Per cent		8.4	.9	.1		1.2	.3			

changing conception of a satisfactory resection. After 1939 we believed that total removal should be sought for.

Tables IV and V are likewise broken into the two six-year periods. They show by years, the number of resections our patients needed in order to obtain what we considered a satisfactory result.

Perhaps a few would like some explanation as to what we call a satisfactory result. The absence of residual urine has never determined a satisfactory result; we demand complete healing, free, painless urination and microscopically negative urine in every patient who had miscroscopically negative urine before resection was commenced, or who had a urological tract not severely damaged by the obstruction.

Tables IV and V also designate whether the subsequent resections were needed by patients having benign or malignant glands and the average interval between these delayed resections in years.

Table VI, a summary of the two previous tabulations, brings out, as did Table III, the decrease in necessity of subsequent resections after 1940.

TABLE VI. ANALYSIS OF SUBSEQUENT RESECTIONS, 1934-1945

Year	Number of Patients Resected	Number of Patients Needing Subsequent Resections, Benign				Number of Patients Needing Subsequent Resections, Carcinoma			
		1	2	3	4	1	2	3	4
		Per Cent	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent
1934 through 1939	269	21.9	5.5	1.1	0.3	2.2	1.8		
1940 through 1945	547	8.4	0.9	0.1		1.2	0.3		
Total	816	15.1	3.2	0.6	0.1	1.7	1.0		

TABLE VII. NUMBER OF PATIENTS CYSTOTOMIZED PRIOR TO PRIMARY RESECTION

Year	Number of Patients Receiving Primary Resection	Patients Cystotomized Prior to Primary Resection	
		Number	Per Cent
1935	42	8	19.0
1936	52	6	11.5
1937	55	15	27.2
1938	55	9	16.3
1939	42	3	7.1
1940	41	6	14.6
1941	61	8	13.1
1942	75	3	4.0
1943	95	3	3.1
1944	114	2	1.7
1945	111	2	1.8
Total	743	65	6.7

Table VII shows a relatively high number of patients who were subjected to cystotomy prior to the primary resection. Cystotomy in general was done for three reasons; (1) The general condition and age of the patient were such that we believed operation might have to be discontinued at any time during the procedure. The suprapubic, being a safety valve, allowed prolonged convalescence with the bladder neck at rest. (2) The gland was of such size that we wished preliminary shrinkage to occur, and a satisfactory result could be obtained by one or two resections. (3) The bladder contained large stones.

Table VII graphically shows our increasing self confidence in our ability to completely remove larger amounts of tissue without increasing the calculated risk.

Table VIII is, in itself, self-explanatory and represents a serious complication of transurethral procedure. This complication, in

TABLE VIII. POSTOPERATIVE COMPLICATIONS, BLADDER PERFORATION AND EXTRAVASATION

Year	Number	Extra Peritoneal	Intra Peritoneal	Operated	Recovery	Death
1937	1	1		1	1	
1940	1		1	1		1
1941	1	1		1		1
1942	1	1		1	1	
1943	1	1		1	1	
1944	2	2		1	1	1
Total	7	6	1	6	4	3

No patients presented above postoperative complications during 1934, 1935, 1936, 1938, 1939, and 1945.

TABLE IX. POSTOPERATIVE INCONTINENCE, 1935-1945

Year	Number	Type of Obstruction Operated			Recovery		
		Carcinoma	Bladder Neck Contracture	Benign Adenoma	Complete	Partial	None
1935	1	1				1 (CA)	
1944	6	1	1	4	5		1 (CA)
1945	3		1	2	1	2	

our hands, was most frequent in contractures of the bladder neck and occurred several times in passing the instrument, the beak of the resectoscope leaving the posterior urethra just outside the internal sphincter. One of the perforations which occurred in 1944 represents the increased risk assumed by the operator when the patient has an excessively large intravesical prostate and a relatively small bladder capacity. The beak of the instrument was caught on a trabeculation while trying to get over the intravesical portion of the prostate and a small tear was made in the posterior bladder wall.

Table IX is remarkable for the relatively small amount of incontinence in the early years, with a marked increase in the past two years. The infrequency is accounted for by our extreme conservatism in the early years. We always left a small amount of visible adenoma in the region of the external sphincter and verumontanum. This occasionally caused adhesions with the formation of double-barrelled urethra which, though healed, sometimes decreased the calibre of the urinary stream, occasionally caused a secondary contracture at this point, and frequently embarrassed the operator by preventing catheterization.

One likes to offer explanations for incontinence. I have always been cynical about anyone classifying incontinence on a complete and partial basis. I have analyzed these patients, and here are the facts.

The one patient in 1935, as you see, was a carcinomatous patient. He had complete control night and morning; he used a clamp during the afternoon and evening.

The one patient in 1944, who did not recover, was also carcinomatous. He is compelled to wear a bag urinal and has stress incontinence at all times when he is on his feet. He is continent when reclining in bed.

Two patients in 1945 had only partial recovery. The first was a seventy-seven year old individual who had 800 c.c. overflow with a chronically infected bladder. A 72 gm. prostate was removed. He now has complete control night and day when sitting. He begins dribbling late in the afternoon when standing and wears a clamp at that time only. In April, 1946, he stated that he was continuing to improve. The second patient in 1945 was a man of sixty-seven who had infected urine, bladder neck contracture and prostatic stones. Initially, there was constant dribbling when standing. In April, 1946, he wrote that he was greatly improved but did not state the exact degree of improvement. However, he was more concerned over insomnia at this time and I judge his incontinence is not marked.

Since we have been completely removing the enlargement, many of these patients have incomplete control for about twelve hours, and following this they regain complete control.

Table X is a record of all deaths associated with the operative procedure. I personally know that many of these patients are not

TABLE X. DEATHS ASSOCIATED WITH TRANSURETHRAL SURGERY OF THE PROSTATE

Year	Number of Patients	Age	Cause	Time P. O.
				Days
1935	1	71	Ac. epididymitis, Sepsis	35
1937	1	66	Uremia	20
	2	78	Cardiac	8
	3	70	Agranulocytosis	21
1938	1	85	Cardiac or embolic	6
	2	75	Cardiac	10
	3	77	Cardiac	2
1939	1	74	Cardiac, secondary to hemr.	2
	2	76	Cardiac	6
1940	1	77	Cerebral thrombosis	2
	2	89	Intra-perit. perf., pneumonia	3
1941	1	76	Periurethral abscess, sepsis	8
	2	70	Perf. bldr., pulmon. edema	5
	3	71	Cardiac or embolic	10
	4	71	Sepsis, cardiac and embolic	25
1942	1	79	Cardiac or embolic	25
	2	72	Aortic sten, ac. bact. endocar.	33
1944	1	70	Uremia	37
	2	81	Perf. bldr. wall abscess	8
1945	1	75	Broncho-pneumonia	23
	2	65	Pulmonary embolus	21
	3	67	Subac. bact. endocar., rupt. ht.	127
	4	75	Pulmonary embolus	3

operative deaths, but I feel that every patient who dies following one of these procedures should be listed. As you will notice in most cases many days have elapsed between operation and death. Many of these deaths occurred suddenly after the patient had made a complete recovery and was home following his usual routine of living.

Table XI is self-explanatory. The mortality percentage of 2.4 is somewhat higher in this series than in other reports with which you are familiar. This increase, I believe, is partially due to the complete-

TABLE XI. SUMMARY

1934-1945	890 Resections
	Per cent
Late hemorrhage	2.1
Extravasation	0.7
Stricture (non-meatal)	0.5
Incontinence:	
Partial	0.3
Complete	0.1
Associated death	2.4

ness and method of computation as many of these patients died some time after being discharged from the hospital. The apparent cause of death simply reflects, I think, the high incidence and degree of degenerative cardiovascular lesions encountered among the patients in this age group in Southern California.

Continued observation during these twelve years of the work of equally experienced resectionists using the electric loop instrument, has strengthened our original convictions that the Braasch-Bumpus resectoscope, in the hands of a competent resectionist, remains on a par with any other resectoscope in its ability to remove large amounts of prostatic tissue rapidly and efficiently.

112 N. Madison Ave., Pasadena 4, Calif.

CYSTOSCOPIC EXAMINATION OF FEMALE DOGS

BENJAMIN B. BARRINGER, M.D.
From the Memorial Hospital, New York, N. Y.

For the past four years at the Memorial Hospital, we have been cystoscoping at various stated intervals some thirty female dogs. Some of these dogs have received alpha-naphthylamine, some beta-naphthylamine crude and purified and some benzidine and benzidine sulphate by oral administration in order to determine the carcinogenic effect of these chemicals upon the bladder. These dogs have been cystoscoped from one to three months or oftener to determine if and when bladder carcinoma occurred. Because we wished not only to observe the bladder but also to obtain specimens for histological examination, we have had to use the large cystoscope (24 F.) capable of carrying the cystoscopic forceps for obtaining specimens. At the commencement of this experiment we were unfamiliar with the technique involved, as we had never before cystoscoped a dog.

Dr. Hueper, whose authoritative work on occupational tumors was published in 1942, has observed and cystoscoped dogs over a long period of time. He was kind enough to give me a brief résumè of his experience and start me on the right road.

My impression is that Dr. Hueper used only the small observation cystoscope and did not attempt to get specimens from the bladders of the dogs which he cystoscoped. Because of various confusing descriptions of lesions seen in the bladders of dogs, tumors, raised areas, ulcerations, congested areas, pre-tumor areas, from the first we determined to check methodically our visual impressions with histological specimens. There was a great deal of trouble in attempting to use a large cystoscope with some of the smaller dogs and we got into some difficulties.

This paper is being written with the hope that we may give enough information to simplify the procedure for any other worker who may need to do cystoscopic examinations on dogs.

Dr. Hueper assured me of one very important detail and that is that dogs do not need any anesthetic while being examined. This

has been proved during the past four years and we can conclude that most dogs suffer little or no pain during the procedure. Any pain they may experience is about comparable to that suffered by any human female patient, and peculiarly enough, when tumors have occurred, the dogs apparently suffer no more pain on cystoscopy than when their bladders are normal. The choice of dogs is important, I only wish this had been realized before we started the work. They should be short haired of medium size or larger, 35 pounds and upwards. They preferably should have had pups. This latter procedure, as in the human female, enlarges the vaginal orifice, thereby making cystoscopy much easier. In all of our dogs as far as we could determine, only one had had pups. Our dogs weighed from 15 to 60 pounds.

The instruments necessary for cystoscopy are both small and large cystoscopes, steel sounds from 18, F. to 25, F. cystoscopic forceps for obtaining specimens and a small bivalve nasal speculum 3.25 inches long for exposing the uretheral meatus. The dog is strapped on the table on her back with the vaginal orifice coming down to the edge of the table. The speculum is introduced and the urethral meatus exposed. This exposure is not an easy procedure if the dog is small. Sounds from 18 F. to 25 F. are now introduced into the urethra. The first dilatations are somewhat painful; this urethral dilatation causes a very slight prolapse of the urethral mucosa, so it can be more readily observed through the speculum. At times the ensuing passage of the cystoscope is a matter of guesswork as the cystoscope entirely fills the space between the blades of the speculum. It is quite probable that a number of times the vagina has been cystoscoped instead of the bladder. In small dogs it is almost impossible to use the 24 F. cystoscope, and one has to have recourse to the small observation cystoscope. If a dog is in heat, the vaginal outlet is a good deal congested and elongated and the speculum often not long enough to expose the urethral meatus. The absolute proof that the cystoscope is in the bladder is the return of urine through the cystoscopic sheath. Of course if a dog has urinated prior to examination we have no such return, but if on turning on the irrigating fluid through the cystoscope, no fluid returns vaginally, we may be sure we are in the bladder.

In human subjects we know that most bladder tumors are on the dependent part of the bladder around the orifices of the ureters. The dependent portion of the dog's bladder, because of her reversed position, is exactly the opposite, that is, the portion of the bladder distant from the ureters. We have no data as to the portion of the bladder in which tumors most frequently occurr, but Hueper found them most often in the vault.

Fig. 1. Dog 13. Hydronephrotic kidney.

We have followed these dogs, observed the appearances of the vesical carcinoma, obtained specimens from such tumors and have had autopsies on the dogs, confirming the diagnoses obtained by examination of specimens obtained through the cystoscope (Fig. 1 and 2). As far as has been observed, there were seen no true papilloma of the bladder, but a number of cases of papillary carcinoma of the bladder, almost always multiply distributed throughout the bladder. We have seen dogs with tumors obstructing both ureters (Fig. 3) the dog dying of uremia from such obstruction. We have seen no carcinoma of the ureter or renal pelvis. Several

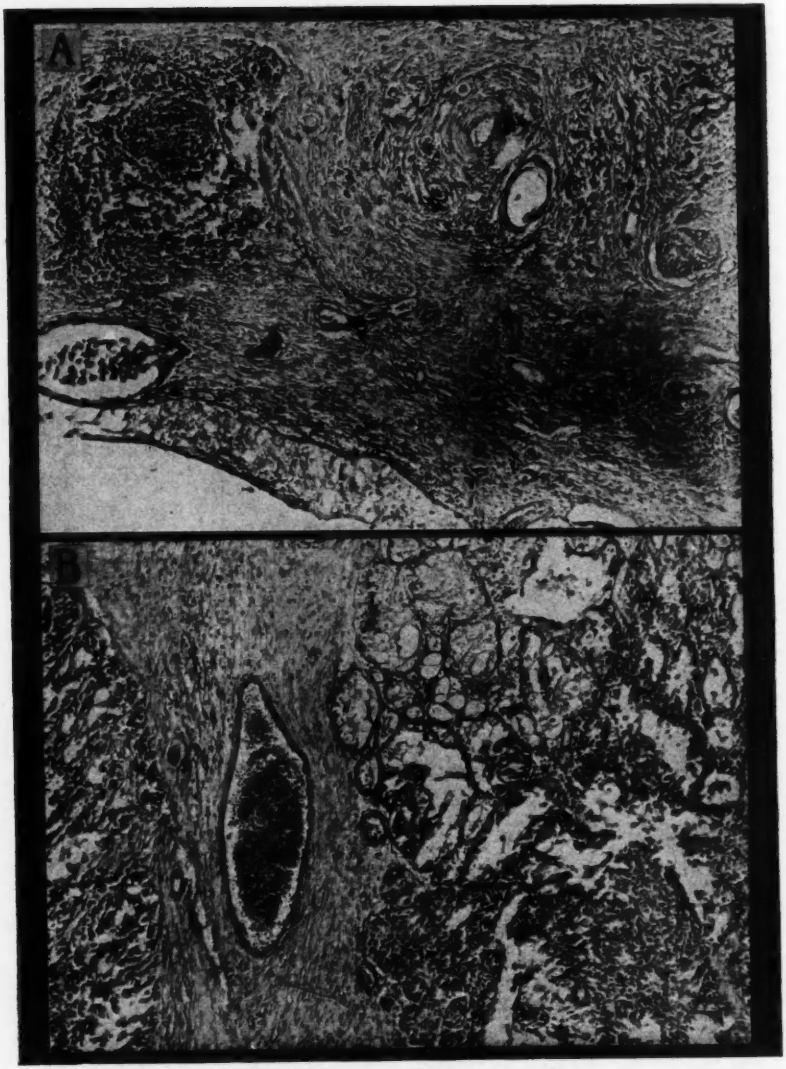

Fig. 2. Dog 13. Carcinoma of bladder. (*A*) Specimen obtained by cystoscopic forceps. *(B)* Autopsy specimen.

times the dogs have lived for very long periods after the original histological diagnosis of bladder carcinoma has been made.

In February, 1945, one dog had a bladder carcinoma, proved by cystoscopy and by histological examination of a specimen removed by cystoscopic forceps. This dog is still living. She has had no beta-naphthylamine since the appearance of the carcinoma.

This brief report is in no way to be construed as other than a description of the cystoscopic procedure and is not a report on the

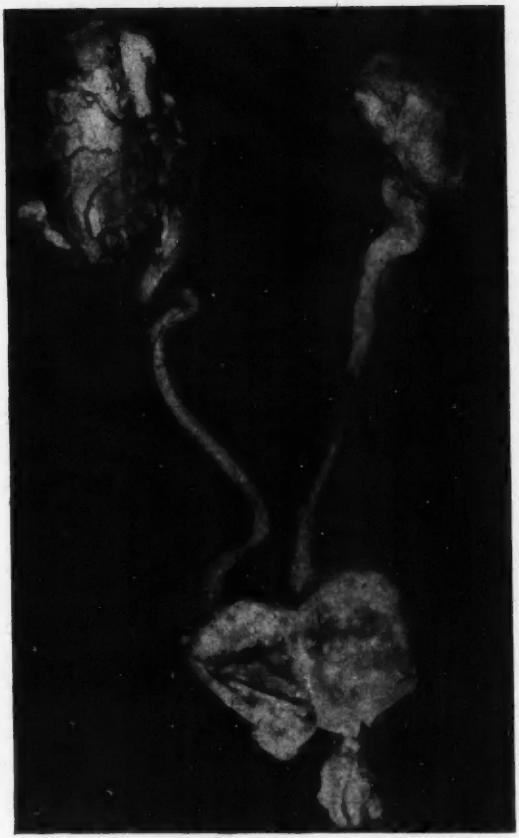

Fig. 3. Bilateral hydroureters and hydronephrosis secondary to bladder carcinoma. Dog died of uremia.

effect of various chemicals used. This will be reported at a later date. Suffice it to say that only in dogs fed beta-naphthylamine have bladder cancers occurred. Benzidine is much more toxic than either beta or alpha-naphthylamine, the bladder showing in the first month of its administration many submucous hemorrhages. Notwithstanding that we have not seen bladder carcinoma in the dogs fed benzidine.

Mr. Bernhard Mecke, administrator of Sloan Kettering Institute, has had entire charge of this work and has assisted in the examination of the dogs. The work would not have been accomplished without his enthusiastic support. My thanks are due him.

114 E. 54th St., New York 32, N. Y.

DISCUSSION

DR. LEON HERMAN (Philadelphia, Pa.): I would like to use Dr. Creevy's presentation and his ingenious adaptation of cystoscopic forceps for the panendoscope as an excuse for the description of a method for the removal of elongated foreign bodies from the bladder that may be original. During the last month we have had a minor epidemic of foreign bodies in the bladder. One of our more imaginative citizens coming home from choir practice one night inserted a swizzle stick in his urethra, Dr. Cunningham has explained the legitimate use of this instrument to me. This stirring episode was marred by the fact that the rod broke and the proximal portion was removed surgically.

Several days later a sixteen-year-old Italian girl appeared with a piece of lead pencil in her bladder.

The case in which we are particularly interested is that of a woman, aged twenty-seven, who consulted a gynecologist on account of marital sterility. She was instructed to take her temperature, per vaginum, in the process of which she lost the thermometer in her bladder. This happened one Sunday morning and the next day we found the thermometer lying diagonally in her bladder, the mercury end being behind the sphincter ring at about five o'clock.

Long and ineffectual efforts were made to remove this when the following method occurred to us. As Figure 1 shows, a large resectoscope has been inserted with the loop fully advanced, and the latter has been threaded onto the blunt end of the thermometer. By bringing the instrument to the midline and manipulating it, the loop, as Figure 2 shows, has been brought slightly beyond the 100° which is red. I may say that at that moment her intravesical temperature was 100° F. At this time we retracted the loop somewhat, thus fixing the thermometer in its grasp and then advanced the instrument, thus carrying the thermometer away from the bladder wall, as shown in Figure 3. It remained to bring the loop near enough to the mercury bulb so that when the resectoscope was rotated, the end of the thermometer would clear the edge of the aperture in the instrument. Having done this, we rotated the resectoscope so that the aperture pointed directly backward.

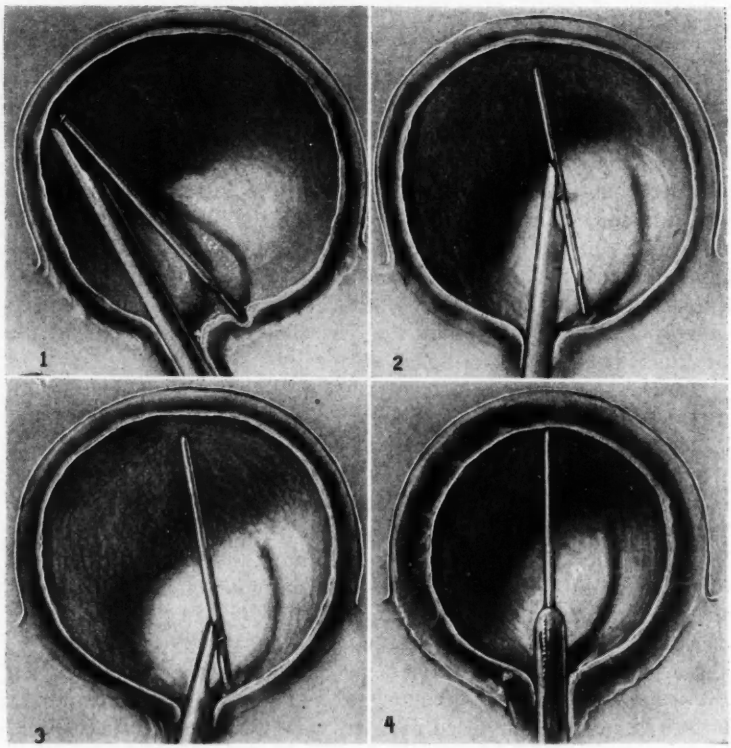

Fig. 1. The fully extended loop of the resectoscope has been threaded over the blunt end of the thermometer.

Fig. 2. The resectoscope has been brought to the midline. The loop has slipped over the thermometer to a point slightly beyond the 100° mark and has been retracted to fix the loop in its grasp. The resectoscope has been advanced thus carrying the thermometer (mercury end) away from the bladder wall.

Fig. 3. The loop has been brought practically through by withdrawal and other manipulations of the resectoscope to a point where the mercury end will clear the edge of the aperture when the instrument is rotated.

Fig. 4. The resectoscope has been rotated so that the aperture is directed backward and the end of the thermometer brought into line with the sheath. By unlocking and slowly withdrawing the working unit the thermometer is "delivered."

The working unit was now unlocked, whereupon the visual field disappeared, the lens aperture having been covered by the mercury end of the thermometer. The latter, forced by intravesical pressure, appeared at the proximal end of the sheath as the working unit was withdrawn.

THIRD DAY, JUNE 22, 1946

THE DIFFERENTIAL DIAGNOSIS OF TUMORS OF THE PROSTATE AND ADJOINING AREAS OF THE RECTUM AND BLADDER BY CHEMICAL ANALYSIS

ARCHIE L. DEAN, M.D., and HELEN Q. WOODARD, Ph.D.

From the Departments of Urology and Chemistry, Memorial Hospital, New York, N. Y.

Patients with tumors of the prostate and adjoining areas of the rectum or bladder frequently present difficult diagnostic problems. Before the possible inhibiting effects of endocrine therapy in prostatic cancers were known, the origin of these growths was of little more than academic interest because the majority were highly malignant, all were inoperable, and, since radiation was ineffective, the life expectancy of the patients was short. Now that the benefits of hormonal treatment of extensive prostatic neoplasms has been demonstrated, it is of great practical importance to know whether these tumors originated in the rectum or bladder and subsequently grew into the prostate, or whether they originated in the prostate and later involved the bladder or rectum.

In the great majority of primary rectal cancers the characteristic microscopic picture is diagnostic, but when the tumor originates in the prostate and invades the rectum pathological examination can reveal only the presence of an adenocarcinoma from some other primary source. Occasionally an adenocarcinoma of the bladder may grow from an area of long standing cystitis close to the prostate and its structure may leave doubt as to its origin. Assays of the serum acid phosphatase are not always helpful because invasion of the prostate from the rectum or bladder might cause an increase of this enzyme while we have found instances in which widespread invasion of the rectum from the prostate had occurred with no significant alteration of the serum acid phosphatase.

In such obscure cases it has been possible to show whether the

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tumor does or does not originate in the prostate by measuring the acid phosphatase activity of extracts of tumor tissue removed through the cystoscope or proctoscope. Admittedly this diagnostic method has only a limited field of usefulness, namely, in those cases in which a rectal tumor springs from the prostate. In these cases, however, by accurately showing the origin of the growth in-

TABLE I. TISSUE ACID GLYCEROPHOSPHATASE, UNITS PER GRAM

Tissue	*Number of Specimens*	*Range of Acid P-ase*
Carcinoma of rectum	4	0.30- 2.6
Rectal mucosa	3	4.44- 1.1
Carcinoma and papilloma of bladder	8	0.15- 2.7
Normal prostate	4	169.0 - 315.0
Prostate the site of benign hyperplasia or chronic prostatitis	14	81.0 -1,800.0
Untreated carcinoma of prostate	3	110.0 - 550.0

formation of great clinical value, available by no other means, is readily provided.

Chemical analysis provides a clear-cut differentiation of these tissues because while normal rectal mucosa and rectal or bladder carcinoma contain acid phosphatase, their acid phosphatase activities are only 1/100 to 1/1000 as great as that of prostate tissue. Table I shows the acid glycerophosphatase activities observed on large (1 to 5 gm.) specimens of tissue obtained at operation or autopsy. Determinations were made by the technique described by one of us elsewhere, sodium-beta-glycerophosphate being used as substrate.

Specimens of prostatic cancer removed from the rectum or bladder are likely to have less acid phosphatase activity than the primary tumor since usually they are somewhat necrotic and they may contain rectal or bladder tissue. Nevertheless, the acid phosphatase activity of prostate tissue is so high that if the activity of a specimen exceeds 10 units per gram it is reasonable to assume that it is of prostatic origin. If a sinus tract extends from the prostate into a rectal or bladder tumor, prostatic secretion might contaminate the specimen and raise its acid phosphatase activity abnormally. Therefore, low acid phosphatase assays are more significant in excluding the prostatic origin of a tumor in an adjoining organ than are high readings in proving the prostatic origin of such a growth.

In the method used for determining tissue phosphatase, extracts are made in 20 c.c. water for each gram of tissue. If specimens are small it is necessary to use 50 to 100 c.c. water for each gram of

tissue to obtain workable volumes. Thus, if 120 mg. of tissue are available, the extract should be made 12 c.c. water for a 1 to 100 dilution. The time of incubation may be lengthened at convenience to compensate for the amount the extract is diluted. Except for changes in dilution and time of incubation the usual technique for large specimens is employed. Determinations made on extracts at dilutions higher than 1 to 100 are usually subject to such large experimental errors that the results are equivocal. Therefore, for reliable results the specimen should be of at least 100 to 200 mg. This amount of tissue can be obtained with three or four bites of the biopsy forceps commonly used through a cystoscope.

The following case report illustrates the usefulness of the method:

D. H. (M.H. 75582) an active real estate broker in West Virginia, fifty-eight years of age, was first seen November 16, 1944, complaining of frequent, pencil-like stools accompanied by severe pain in the rectum. The man had been apparently well until September, 1944 (two months previously), when the present illness began. He promptly consulted his family physician who referred him to a clinic in another city. Here he was carefully examined, and after an exploratory laparotomy had been performed, the diagnosis was made of an inoperable adenocarcinoma surrounding the rectum and involving the prostate and seminal vesicles. No treatment was suggested. A month after his discharge he came to the Memorial Hospital. Rectal examination showed an annular stricture of the lower rectum with considerable ulceration but complete insertion of the examining finger was impossible. Bimanual examination under spinal anesthesia showed a large pelvic mass, the upper limits of which could not be reached. The growth definitely involved both the prostate and rectum but no details regarding the size, shape or consistence of the prostate could be determined. Endoscopic examination showed 30 c.c. clear residual urine and a moderate generalized congestion of the trigone and prostatic urethra with no ulceration or edema. There was no significant intrusion of the prostate at the bladder outlet.

General physical examination showed a middle-aged man in apparently good health except for a dense mass of enlarged lymph nodes in the left supraclavicular fossa. Urinalysis showed specific gravity 1.020, acid reaction, yellow color, no albumin, no sugar, microscopically a few epithelial cells. Hemoglobin was 86 per cent, red blood cells 4,400,000, white blood cells 10,600, polymorphonuclear leukocytes 50 per cent, monocytes 12 per cent, lymphocytes 38 per cent. Prothrombin, 78 per cent. Serum bilirubin 1.1 mg. per 100 c.c., serum total calcium 9.6 mg. per 100 c.c., serum acid phosphatase 1.8 units, serum alkaline phosphatase 2.1 units, serum inorganic phosphorus 3.02 mg. per 100 c.c., blood sugar 92.6 mg. per 100 c.c., and blood urea nitrogen 12.1. Excretory urograms showed good excretion in five minutes. There were no

visible abnormalities of kidneys or ureters and no evidence of obstruction. Roentgenograms of lumbar spine, pelvis and lungs showed no evidence of disease.

Biopsy from rectum showed adenocarcinoma, grade 3, infiltrating the rectal mucosa from some other presumably primary source. Assay of tumor tissue removed from rectum showed acid glycerophosphatase 39 units per gram, alkaline 0.05 units per gram, findings characteristic of prostatic phosphatase. Since the patient's rectum was seriously obstructed colostomy was performed and he was castrated. He was discharged nineteen days later greatly improved. At this time the acid phosphatase had decreased to 0.78 units and the alkaline to 1.7 units.

While free evacuation of the bowels and termination of rectal pain played a major role in improving this patient's health, there was also a rapid diminution in the size of the pelvic mass and the metastatic nodes in the left supraclavicular fossa. As a result the man was able to resume his previous occupation shortly after returning to his home. He continued well and his phosphatase assays remained normal until February, 1946, fifteen months after castration when the acid phosphatase rose to 1.4 units although the alkaline remained within normal limits at 214 units. At this time he was given 0.25 mg. of estinyl daily. Although a relapse has occurred following castration, and no significant improvement has followed the administration of estrogens, this patient still conducts his business daily and is comfortable except for slowly increasing edema of the external genital organs and the right lower limb. Presumably he will succumb to prostatic cancer but at this time he has enjoyed twenty-two months of productive life. We believe that the phosphatase assay of the rectal tumor was useful in indicating the origin of the growth in the prostate and suggesting the rational type of treatment.

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MUCINOUS ADENOCARCINOMA OF THE BLADDER

F. S. PATCH, M.D., and J. E. PRITCHARD, M.D.

From the Department of Urology and Pathology, The Montreal General Hospital, Montreal, Que.

In 1935, in association with the late Dr. L. J. Rhea, a paper was published which dealt with the development of Brunn's nests and their relation to cystitis cystica, cystitis glandularis, and mucinous adenocarcinoma of the bladder. One case of mucinous adenocarcinoma was reported.

Recently, Ackerman reported a mucinous adenocarcinoma of the pelvis of the kidney, whose development the author ascribed to a glandular type metaplasia.

The publication of Ackerman's paper has stimulated us to review the subject of mucinous adenocarcinoma of the bladder, and to report two other cases observed since the first was published.

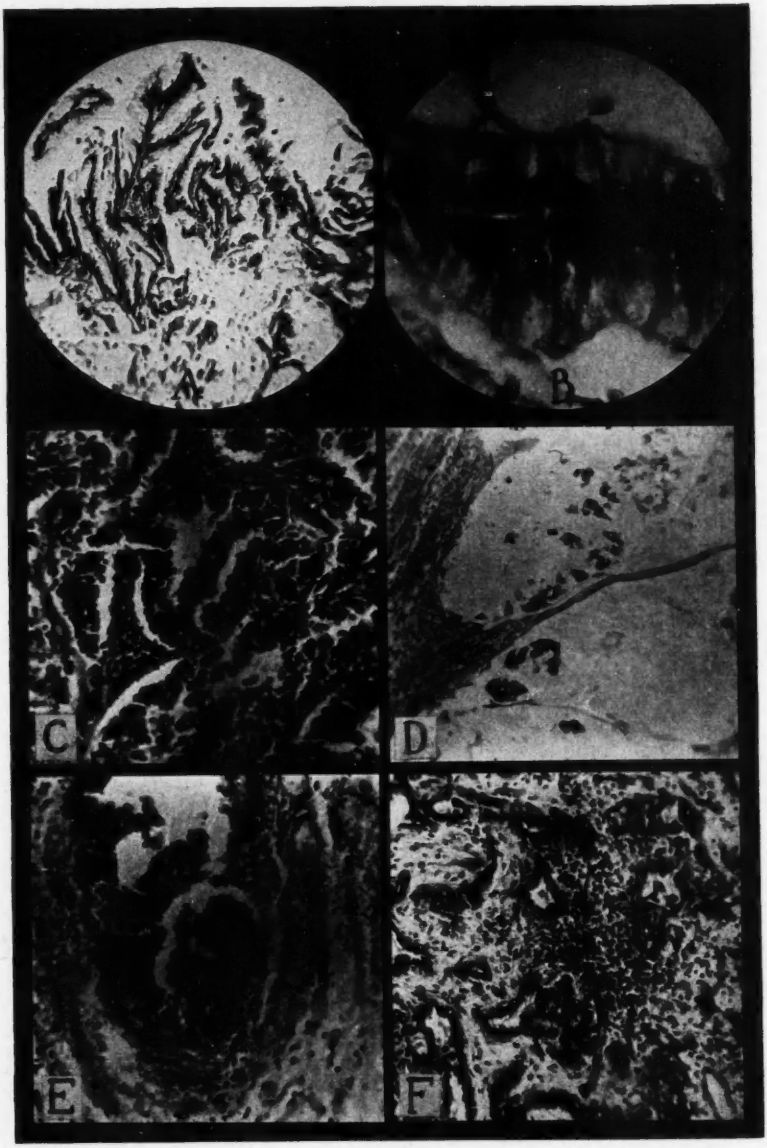
CASE REPORTS

Case 1.—An unmarried woman, aged sixty-seven, was admitted to the service of one of us (F. S. P.) on April 23, 1931 (M.G.H. No. 2306/31). She gave a history of having had pain in the lower abdomen for ten years, increasing frequency of urination, by day seven to eight times, by night two to four, burning micturition, and terminal pain. Hematuria, including two profuse hemorrhages, had occurred during the last two months. She had lost 20 pounds in the previous six months. Frequency had recently become very troublesome, occurring every one-half hour in the daytime.

A mass was palpable in the bladder region suprapubically. The urine was moderately purulent, and was noted as "slimy."

Cystoscopy revealed a universally inflamed bladder, with a sessile tumor at the upper extremity of its base.

An exploratory suprapublic operation was performed May 1. A sessile tumor was noted at the postero-inferior aspect of the bladder. Its surface was covered with a mucoid material. Similar material was noted on the bladder base, and around the base of the tumor, collected in large globules, "sticky and tenacious in character." The mass could be palpated through the peritoneum. The peritoneum was opened and the mass was found to have extended through to the peritoneum, and to be confluent with a mass in the tip of the appendix. The fundus uteri was also involved or adherent to the mass. The peritoneum was closed, the


A
B
C
D
E
F

bladder tumor burned with the diathermy current, and the bladder drained with a permanent suprapubic catheter. The patient was allowed to go home, was more comfortable for a period, but died a year later. No autopsy was secured.

Pathological report: "M.G.H. S-31-664 (Dr. L. J. Rhea). The specimen consists of a small amount of tissue which was placed in fixing fluids at once. After fixation it was embedded in paraffin, and microscopic sections were made and stained with various stains. The tumor is composed of glandular structures with a scanty supporting connective tissue framework in which there are small blood vessels, most of the glands have smooth walls, but some of them show papillary projections into the lumina. There is a large amount of material which, when stained with muci-carmine, gives the staining reaction of mucin. The epithelial cells of the tumor vary a gerat deal in their characters, but most of them are tall and have their nuclei at their bases. Mucin is seen within many of these cells, gland acini, and diffusely distributed through the section. The amount of mucin in the epithelial cells varies. In some there is only a small amount, situated in the cells' substance nearest the gland lumen. In others, there is a large amount of mucin, which distorts the cell, producing the so-called goblet cells. Between these two extremes, there are all gradations. Microscopic diagnosis: Mucus-secreting adenocarcinoma" (Fig. 1, *A* and *B*).

Case 2.—A widow, aged sixty-eight, noticed blood stains on her clothing after urination for several months. During this time, she had observed an increased frequency of urination, both by day and night, with some burning on urination. The day before her admission to the Western Division, The Montreal General Hospital on November 1, 1942, there was profuse hematuria (W. D., M.G.H., No. 3478/1942).

Cystoscopy revealed a non-papillary sessile tumor, covered with a membranous layer, situated on the upper and posterior surface of the bladder.

The tumor appeared to be ideally situated for resection, and operation was performed on November 5, 1942, under spinal anesthesia. When the bladder was opened, the tumor was larger than had been surmised and had infiltrated to the perintoneum. On opening the peritoneum, projecting knobs of the tumor were visible on the peritoneal surface of the bladder, although the perintoneum seemed intact. A combined intraperitoneal and intravesical resection was performed with the cautery

Fig. 1. (opposite page) Case 1. *(A)* Area in a primary adenocarcinoma of bladder. Note papillary arrangement of tumor, covered with tall columnar epithelial cells; cytoplasm pale due to mucin in them. *(B)* High power view of tumor, showing tall columnar mucus-containing epithelial cells, with basally placed nuclei.

Case 2. *(C)* Solid areas in tumor, showing mucin-secreting adenocarcinoma. *(D)* Showing large mucinous lakes, with clumps of viable carcinomatous cells floating in fluid. *(E)* Single Brunn's nest with early lumen formation, with secretion of mucin.

Case 3. *(F)* Area of tumor, showing mucinous adenocarcinoma.

knife, about ¾ inch from the tumor edge. The peritoneal edges were sutured and the bladder closed around a mushroom catheter.

The postoperative course was uneventful, except for a rather slow closure of the suprapubic fistula.

The bladder was examined cystoscopically from time to time. At no time was there any evidence of recurrence in the bladder.

The increased frequency of urination, which had abated following the operation, returned in the course of the next year. Fifteen months after the operation, her physician discovered a mass in the lower abdomen. Bladder examination was negative. X-rays showed changes in the upper lumbar vertebrae suggestive of metastasis.

She gradually failed and died three months later. Ascites had developed, and paracentesis had to be used on several occasions. An autopsy was not obtained.

Pathological report: "M.G.H. S-42-875 W. D. (Dr. L. J. Rhea). Specimen consists of bladder wall and tumor measuring 7.5 by 2.5 cm. Externally, the wall is smooth and glistening, there is one 4.0 by 2.5 cm. oval area of hematoma, the rest is very injected. There are three soft, nodular areas, one measuring about 0.7 cm. in diameter. On section these nodules contain a very soft, friable, translucent, almost jelly-like material. The inner aspect is composed mainly of a 5 cm. diameter tumor which has heaped-up wide edges and a crater-like centre. The base is firm, but the more superficial tissue is very soft, friable, bloody and deeply injected. Microscopic: Section through gelatinous nodule on external surface of bladder shows a fibrous wall enclosing a mucoid mass throughout which there are many clusters of carcinoma cells, some of which have no visible cytoplasm. Others have a small amount of pale staining cytoplasm and still others are large, with an abundant vesicular cytoplasm, obviously containing mucus. In some of the clusters there is a ring formation suggesting glandular structure. Sections through the whole thickness of the bladder show an intact mucosa which is hyperemic and mildly infiltrated with lymphocytes. As the section is traced along, the mucosa abruptly becomes replaced by a solid mass of carcinoma composed of small polygonal cells, many of which contain mucus. In this part there is no definite glandular arrangement, but here and there, there is a columnar arrangement of alveolar cells suggesting glandular structure. The whole thickness of the bladder wall is permeated by tumor which in many places is as already described, but in other places there is a distinctly columnar cell adenocarcinoma with mucus secretion. In the outer coats the tissue consists chiefly of mucus masses supported by thin strands of connective tissue and in which there are small clusters of mucus-secreting carcinoma cells. In certain fields on the microscope, there are no visible epithelial cells, only mucus and strands of connective tissue. Microscopic diagnosis: Columnar cell, mucus-secreting adenocarcinoma of the bladder" (Fig. 1, *C*, *D* and *E*).

Case 3.—A man, aged sixty-six, was admitted to the Central Division,

The Montreal General Hospital, October 12, 1937 (M.G.H. No. 5807/1937 C.D.). He had been complaining of increased frequency for two years, and dribbling urination. His physician found pyuria, and an enlarged prostate. His prostate was enlarged and hard. Moderate residual urine was found. However, cystoscopy revealed that, in addition to the enlarged prostate, he had a sessile tumor situated on the right postero-inferior surface of the bladder close to the ureteral orifice. A suprapubic operation was performed October 25, 1937. The tumor was about 1 inch in diameter, rough and hard and infiltrating the orifice. It was treated with diathermy. The prostate was noted as being very hard. Later (November 15, 1937) the prostate was removed suprapubically. It was very hard and enucleation was made partly by finger, but mostly by rongeur forceps.

The postoperative course was uneventful. The patient's symptoms were relieved and he was discharged on December 22, 1937. No information is available as to his subsequent progress. All traces of him have been lost.

Pathological reports: "1. Bladder tumor, M.G.H. S-37-1989 (Dr. L. J. Rhea). Microscopic examination consisted of a small piece of tissue received for examination. Section consists entirely of a carcinomatous tumor growing in a connective tissue stroma showing considerable variation in structure. In places there is a diffuse infiltration with pleomorphic, hyperchromic, polygonal cells. In other places, the cells are arranged in anastomosing cords and throughout the tumor there is irregular gland formation, lined by irregular polygonal and columnar cells, showing marked pleomorphism and hyperchromatism. In the glandular structures some of the cells are vacuolated, but no typical goblet cells are seen. There is an eosinophilic and in places, slightly basophilic staining material in the glands. The muci-carmine stain gives the mucus reaction in the cells and secretion. Diagnosis: Mucus-secreting adenocarcinoma of the bladder (Fig. 1, *F*).

"2. Prostate, M.G.H. S-37-2138 (Dr. J. E. Pritchard). Specimen consists of sixteen fragments of prostatic tissue with a total weight of 11.2 gm. The larger of these are globular, capsulated structures, moderately firm in consistency and have a homogeneous white appearance on cross section. Several of the smaller fragments have a firmer and multinodular structure. Microscopic: Some of the fragments show a mild adenomatous type of hyperplasia. At many points there is an alteration in the glandular epithelium from the tall columnar type to a more polygonal form, with relatively less cytoplasm and a large nucleus. In many places this type of epithelium is stratified up to layers of eight or ten cells thick. In one enlarged alveolus this type of reaction lines it completely and there are many free cells in the lumen, mingling with "amyloid bodies." In certain areas there are nests of these atypical cells closely packed and surrounded by a zone of young loosely arranged connective tissue. The impression is that these are carcinomatous alveoli with surrounding reactive fibrosis. Scattered in the stroma of the gland

are distorted columns of carcinoma cells lying in tissue spaces. In other places lymphatic vessels and venules are plugged with tumor cells. There is no distinct adenocarcinoma. The appearance is that of intro-alveolar carcinoma with extension into the stromal tissue, lymphatics and veins. There is no obvious mucus secretion as seen in H and E sections. Muci-carmine stains were not done. Diagnosis: Alveolar carcinoma of the prostate; adenoma of the prostate."

One must consider this a primary alveolar carcinoma of the prostate and that this is a case of two primary tumors, one in the bladder and the other in the prostate.

As far as the treatment of these three cases is concerned, the only point of interest is to be found in the second case. In this case a resection of the tumor with the adjacent peritoneum was carried out, without recurrence of the tumor in the bladder being noted during the eighteen months she survived following the operation.

The two cases in which postoperative observation was possible were extremely malignant, and infiltration of the bladder wall and development of metastases followed rapidly.

The three cases are the only instances of adenocarcinoma of the bladder to be found in the records of The Montreal General Hospital.

Geraghty reported (1918) the occurence of two cases of adenocarcinoma in 182 cases of tumors of the bladder admitted to the Johns Hopkins Hospital, without making any mention of the question of mucin-secretion.

Geraghty, in the report referred to, stated he had seen a case of colloid carcinoma, developing in the exstrophied bladder of a forty-eight-year-old patient. The tumor was diffuse and ulcerating and involved the abdominal wall. He referred to a similar case described by Clado, a rapidly developing tumor with invasion of adjacent structures. It may reasonably be inferred that both these cases were of the same type as the ones we are discussing.

The tumor, a mucinous and adenocarcinoma of the kidney pelvis reported by Ackerman, developed in a man of sixty-six, who had suffered from kidney infections and calculi for fourteen years. The man lived for six years after nephrectomy. At autopsy, metastatic deposits were found involving the peritoneum, liver, other abdominal organs, and the pleura. An interesting finding was of stones in the remainig kidey with squamous metaplasia of the pelvic epithelium.

Ackerman cited a case of Plaut, similar to his own. These constitute, according to Ackerman, the sole instances reported in the literature of this type of tumor occurring in the pelvis of the kidney. He concluded that they were metaplastic in origin. It is worthy of note that not only was the metaplasia of the glandular type, but in part it was squamious in character.

According to Ackerman: "Every section showed alteration of the lining epithelium of the pelvis, which in turn showed all changes from chronic inflammation with fairly normal overlying epithelium to extreme alterations. Some areas showed slight squamous metaplasia, and this gradually underwent transition to zones where the epithelium became slightly piled-up and individual cells began to be vacuolated. These vacuoles contained mucin and became more prominent and numerous until the epithelium resembles that seen in the large bowel."

The resemblance between the photomicrographs of his case and those of our first case is very striking. They are, in fact, almost identical.

It may be proper to refer briefly to the question of the development of this type of bladder tumor which was discussed at length in the paper published by the late Dr. L. J. Rhea and myself in 1935.

Two theories are advanced to explain their development: first, that these tumors are due to developmental inclusions from the intestinal tract; second, that they are of metaplastic development, on the basis of a cystitis cystica and cystitis glandularis, as a result of chronic inflammation, a theory advanced by Stoerk and Zuckerkandl.

The frequent occurrence of adenocarcinoma in exstrophic bladders (Gayet reported fifteen examples in twenty-one cases) was thought to be conclusive evidence of the theory of embryological inclusion. However, the examination of exstrophic bladders of newborn infants showed a normal epithelium without any sign of glandular inclusions (Enderlen and Formiggini).

It is noteworthy that chronic inflammation develops very rapidly on the exstrophic bladder and that metaplastic developments are common, leukoplakia on the one hand, and cystitis cystica and cystitis glandularis on the other; frequently the two conditions are found in conjunction.

It is generally agreed that a further development of the meta-

plastic process may lead from leukoplakia to squamous celled carcinoma. We believe that a similar change from cystitis glandularis to a mucinous adenocarcinoma may occur.

The case reported by Ackerman and that of Plaut, which Ackerman cites, occurring in the kidney pelvis, rather support the supposition that this type of tumor is metaplastic in development, rather than an embryological inclusion.

Though pyelitis cystica has been noted frequently, the only reported instances of the occurrence of pyelitis glandularis of which we are cognizant are those reported by Paschkis (1913) and Brutt (1924).

The whole subject of adenocarcinoma of the bladder is worthy of a more intensive study than we have been able to give in this communication.

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CARCINOMA OF THE BLADDER: A CLASSIFICATION OF EPITHELIAL TUMORS AND A STUDY OF THE EFFECTS OF EXTERNAL RADIATION

FLETCHER H. COLBY, M.D., and RONALD C. SNIFFEN, M.D.

From the Urological and Pathological Services of the Massachusetts General Hospital, Boston

Epithelial tumors of the bladder have shown great differences in their response to external radiation with the 1200 kilovolt unit. Certain tumors disappear or regress appreciably, while others seem little, if at all, affected. A microscopic study of treated tumors was made to determine whether the varying histologic patterns in these neoplasms could be correlated with the difference in response to x-ray treatment.

The following classification has been used at the Massachusetts General Hospital for the past six years:

Papillary Tumors	*Non-papillary Tumors*
Grade 1 A	Grade 1 B
Grade 2 A	Grade 2 B
Grade 3 A	Grade 3 B

In essence it is the same as that used by the Bladder Tumor Registry, as outlined by Dart and Ash.[1,2] A fairly accurate prediction of the histologic makeup of the tumor can be made by gross examination during cystoscopy, but the type and grading are based entirely on the general microscopic morphology of the tumor.

The tumors are classed as (A) papillary and (B) nonpapillary, and then graded according to Broder's method. This classification correlates the gross and microscopic appearance of these neoplasms.

Since the bladder is lined by transitional epithelium, obviously a carcinoma of this organ will simulate in varying degrees this type of epithelium, depending on the differentiation of the tumor. There seems to be no difference in cell type between the papillary and nonpapillary tumors, the distinction rests entirely on cell arrangement. Very few true epidermoid carcinomas with epithelial pearl formation have been encountered in this series, and no adenocarcinomas were included.

Fig. 1. *(A)* Carcinoma of bladder, 1 A. *(B)* Carcinoma of bladder, 2 A. *(C)* Carcinoma of bladder, 3 A.

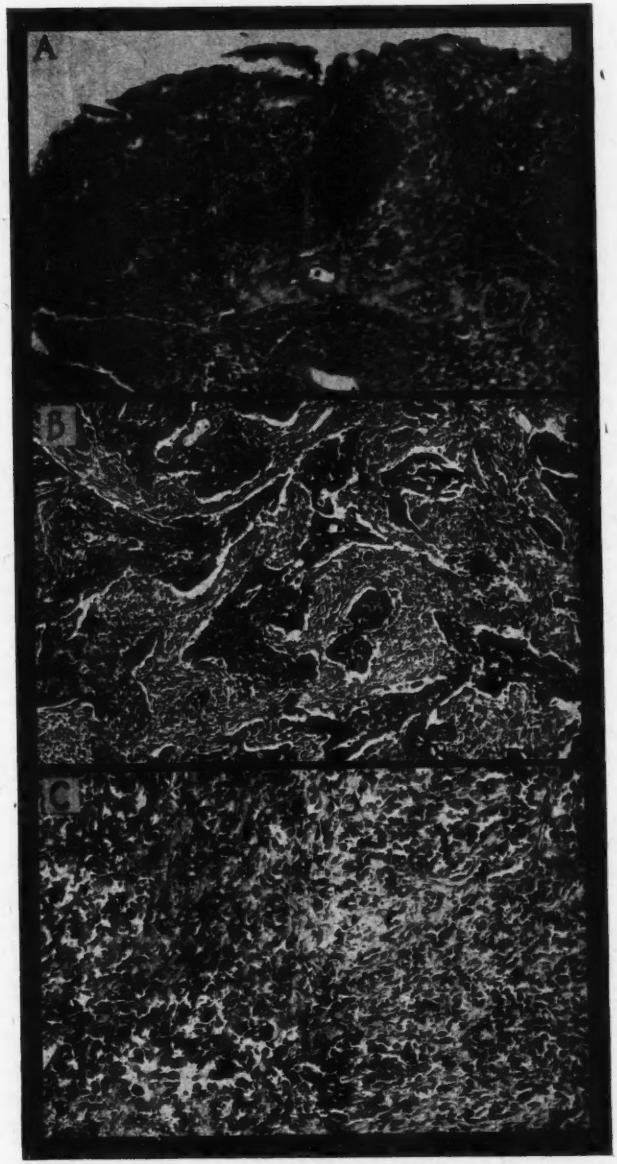

Fig. 2. *(A)* Carcinoma of bladder, 1 B. *(B)* Carcinoma of bladder, 2 B. *(C)* Carcinoma of bladder, 3 B.

PAPILLARY TUMORS

Grade 1 A.—Histologically this tumor is composed of delicate villi covered by morphologically normal transitional epithelium supported by a fine core of fibrous tissue containing capillary loops (Fig. 1, *A*). This is the common papilloma of the bladder. The term "papilloma" is avoided in this hospital because the subsequent behavior of the bladder mucosa cannot be predicted. They are, therefore, regarded as carcinomas.

Grade 2 A.—In this bracket the tumors show unmistakable signs of malignancy, although the papillary character is retained and the villi are covered by recognizable transitional epithelium (Fig. 1, *B*). Lack of differentiation of the tumor is revealed in the slight loss of cell polarity, the heaping up or decrease in the cell layers covering the villi, occasional fusion of neighboring villi, and increased mitotic activity. Occasionally disorganization of a villus and invasion of the stalk are observed. Various form of cell degeneration may be found.

Grade 3 A.—All highly undifferentiated tumors that retain a vestige of their ability to form papillary projections are placed under this heading (Fig. 1, *C*). In short, they exhibit an exaggeration of the malignant qualities mentioned in Grade 2 A with the addition of such features as cell and nuclear gigantism, multinucleation, almost complete loss of cell polarity, and a marked tendency to become necrotic.

NONPAPILLARY TUMORS

Grade 1 B.—In this group diagnostic difficulties present themselves, for it may be hard to decide whether the lesion is neoplastic or merely an epithelial hyperplasia resulting from chronic irritation. The tumor consists of buds and columns of epithelial cells dipping into the underlying tissue. The cells are closely packed and polygonal, without the well defined basal layer and varying cell forms seen in normal transitional epithelium. There is little mitotic activity (Fig. 2, *A*). Proof of the neoplastic quality of the lesion can be determined at times only by clinical observation. Only one tumor of this grade was encountered in our series primarily because this tumor is usually treated by means other than 1200 kilovolt radiation.

Grade 2 B.—Microscopic examination shows a wide departure from the well-differentiated tumors in Grade 1 B, yet the arrangement of the infiltrating cells is such that one can readily recognize their origin from stratified epithelium. The cells are atypical, with variation in size, shape, and staining quality. The nuclei are large in proportion to the cytoplasm, the nucleoli are prominent, and mitosis is fairly frequent. The cells are grouped in columns and masses, with no suggestion of papillary architecture (Fig. 2, *B*). Infrequently these tumors may be true epidermoid carcinomas with prickle cells and cornification.

Grade 3 B.—The rapidly growing, undifferentiated tumors showing no tendency to form papillae are placed under this heading. The cells have no definite arrangement and little intervening stroma. The histologic differentiation is so slight that one cannot determine the origin of the tumor with accuracy (Fig. 2, *C*).

The morphology of all these tumors remained constant throughout treatment, with one or two exceptions where there was a tendency toward further undifferentiation. At times a papillary tumor when it invaded the bladder wall lost its distinctive character and became indistinguishable from a nonpapillary tumor.

We were able to study the tumors of twenty-six patients who had adequate biopsies before, and at least once after, the institution of radiation therapy. These were compared in an attempt to detect any specific changes in radiation degeneration. The conclusion reached was that the histologic diagnosis of "radiation reaction" is little better than guesswork. Changes described in the literature, and seen in our sections, are present in both tumor cells and stroma. The cells show cytoplasmic swelling, distortion, granularity, hyalinization, or vacuolation. The nuclei are large with prominent clumps of chromatin, or are pyknotic. The cells often lie in groups and have ill defined cytoplasmic membranes so that each group superficially resembles a syncytium. The stromal cells usually lay down more collagen or unusually become hyalinized. Lymphocytes, plasma cells and eosinophils appear or, if already present, increase in number. In the blood vessels there may be endothelial swelling, endarteritis and thrombosis. In analyzing the twenty-six cases, it was found that six tumors showed the changes in epithelial cells and stroma enumerated above after radiation therapy had been given, and two cases showed a "radiation reaction" in cells and stroma,

even though therapy had not been initiated; one case was doubtful. Four tumors showed no change in the epithelial cells after radiation, but there were stromal alterations such as the appearance of, or increase in lymphocytes, plasma cells, eosinophils or stromal hyalinization. In four cases no tumor remained after radiation and in this event the biopsy showed a normal epithelium covering granulation

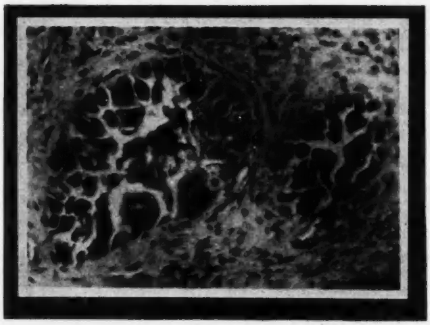

Fig. 3

tissue of varying collagen content with infiltration by lymphocytes, plasma cells and eosinophils; there was no detectable blood vessel change. Nine cases exhibited no histologic change in either cells or stroma after radiation. It seemed to us that the stromal changes after radiation were unpredictable and that if one must give an opinion on "radiation reaction" the most arresting changes appear to lie in the peculiar swelling, distortion and degeneration of the epithelial cells. It is a little amusing, however, that the diagnosis of "radiation reaction" was made on two tumors before therapy had been instituted. Furthermore in practically any rapidly growing neoplasm one can find cytoplasmic and nuclear evidences of degeneration similar to those mentioned above. So far as we could determine the only distinctive, but inconstant, feature of "radiation reaction" lay in the rather amazing proportions the cytoplasmic swelling assumed in the tumor cells. Such degenerative changes were observed from one month to one year after the completion of treatment and did not seem to depend on the amount of radiation received by the tumor (Fig. 3).

External radiation for the treatment of carcinoma of the bladder

with the 1200 kilovolt unit was started by us at the Collis P. Huntington Memorial Hospital nearly nine years ago under the direction of Dr. Richard Dresser. It has been continued at the Massachusetts General Hospital under the guidance of Dr. George W. Holmes. It was found that certain epithelial tumors of the urinary bladder responded favorably to this method of treatment. Only

TABLE I. CLASSIFICATION AND RESULTS OF TREATMENT

Papillary Tumors			Non-papillary Tumors		
Grade	Number Treated	Regressed	Grade	Number Treated	Regressed
		%			%
1 A	4	25	1 B	1	100
2 A	25	24	2 B	12	42
3 A	23	52	3 B	46	30
Total	52	36		59	34

those tumors which were not suitable for local destruction, excision, or radium implantation were treated by external radiation and this has continued to be our policy. In the early cases 7200 r to 8400 r were given at the rate of 300 r to 400 r daily. Additional courses of 2400 r to 4800 r were frequently given in these earlier cases, so that total radiation often amounted to 13,000 r or more. At the present time we give a total of 6000 r through anterior and posterior ports, in daily doses of 300 r and give subsequent treatments only if severe symptoms such as bleeding recur. This is because most tumors seem to respond as well to these smaller doses and because we are concerned about the late deleterious effects of large amounts of external radiation.

One hundred and thirty tumors of the bladder treated by external radiation with the 1200 kilovolt unit were suitable for study. In all but four instances, tissue from portions of the tumor were removed for microscopic examination during cystoscopy or exploratory operation. In nine cases the tissue was inadequate for classification and in six additional cases biopsy proved that the lesion was sarcoma, lymphoma, adenocarcinoma, or metaplasia. This left 111 epithelial tumors which could be classified and graded.

These neoplasms were about equally divided between papillary and nonpapillary (Types A and B). Those of low malignancy were infrequent, as a rule, since such new growths were treated surgi-

cally. The four papillary tumors of lowest malignancy were so extensive that they nearly filled the bladder. Non-papillary tumors of high malignancy (3 B) were the commonest, and since this type of tumor is the most difficult to treat surgically, external radiation was often employed. In fifty, or over one-third, of all these cases the tumor had already spread beyond the bladder at their initial treatment, as proven by positive lymph nodes, x-ray evidence of metastasis, or a large mass in the pelvis.

Well marked tumor regression occurred in a sufficient number of these advanced cases of malignant disease to make us feel that external radiation is a useful palliative agent. We have never advocated it as a cure for cancer of the bladder or considered it a substitute for surgery. We have defined "regression" to mean that the tumor has either disappeared, as viewed through the cystoscope, or has so diminished in size that its remnants can be treated by local destruction or radium implantation, methods impractical before the external radiation. This rigid standard avoids any question of minor changes. The papillary and non-papillary tumors responded about equally well to treatment. Thirty-six per cent of the papillary tumors regressed and 34 per cent of the nonpapillary tumors regressed. Large papillary tumors of low malignancy responded poorly to external radiation as a rule, although one of particularly delicate architecture practically disappeared after 13,000 r. The papillary tumors of high malignancy (3 A) responded well, and about one-half of them regressed to a considerable extent. The relatively poor effect of treatment on the papillary tumors of moderate malignancy (2 A) was disappointing. They have always been most difficult to treat since they are often multiple and "recur" in many places on the surface of the bladder. Total cystectomy seems the best answer to this problem. Our only nonpapillary tumor of low malignancy (1 B) situated on the trigone responded well, as did similar tumors of moderate malignancy (2 B). Of the highly malignant nonpapillary tumors (3B) about one-third responded favorably and it was in this type of neoplasm that the most spectacular regression occurred. Many such growths had probably already spread beyond the bladder.

As one would expect, the end results in such a series of cases of cancer has been poor. Seven cases, 5 per cent, have survived a five-year period tumor free, but in all save one, other methods of treat-

ment than external radiation also were employed. However, distressing symptoms have been alleviated in at least one-half of our patients, they have been made more comfortable, and perhaps their lives have been prolonged.

CONCLUSIONS

A classification of bladder tumors is presented which correlates the cystoscopic and histological characteristics of these neoplasms. One hundred and thirty tumors of the bladder, not suitable for surgery, were given external radiation with the 1200 kilovolt unit. Some of these tumors responded well, others showed little or no response. A study of the histology of the tumors gave no clue as to why this was so. Papillary and nonpapillary tumors responded about equally well and the tumors regressed in one-third of the cases. Symptoms were relieved in about one-half. We believe that the histologic changes described as "radiation reaction" are in no way typical since they occur before and inconstantly after radiation therapy has been given.

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DISCUSSION

DR. HUGH JUDGE JEWETT (Baltimore, Md.): There are two undesirable features in existing classifications of infiltrating carcinoma of the bladder. In one, the categories are so broad that each includes more than one type of tumor. In the other, the categories are so rigid that tumors which are not homogeneous cannot be squeezed into them without sacrificing accuracy. Dr. Colby's classification should prove workable because it is elastic. A year ago, Dr. Sam S. Blackman, of our Department of Pathology, and I made a critical study of ninety-seven autopsy cases of infiltrating carcinoma of the bladder in which pretty large blocks had been removed for sections. We found in 55 per cent of ninety-seven cases there was definite variation in the degree of cellular differentiation throughout the available sections. Since variation in the degree of differentiation throughout a single tumor makes classification upon that basis impossible, it seems obvious that infiltrating carcinoma of the bladder cannot be so classified with any degree of accuracy.

I should like to show a few slides.

[Slide] This is a typical papillary carcinoma, about which I don't believe there is any question.

[Slide] This is another area of the same tumor, the same slide, in fact, which is moderately differentiated epidermoid carcinoma and contains two epithelial pearls on this end.

[Slide] Here is a slide showing papillary carcinoma along the lower border and epidermoid carcinoma just above.

[Slide] This is a higher magnification of the papillary carcinoma of the same tumor, and it is moderately differentiated.

[Slide] Here is a poorly differentiated papillary carcinoma which I believe is easily recognizable even at that distance.

[Slide] This is another case showing a highly differentiated epidermoid carcinoma packed with keratin, almost like skin.

[Slide] Here is another area of that same tumor showing a very poorly differentiated epidermoid carcinoma.

[Slide] This is an example of poorly differentiated epidermoid carcinoma.

[Slide] Here is a totally undifferentiated carcinoma of the bladder with no papillary or epidermoid patterns.

[Slide] Now, it stands to reason, then, that one little biopsy section, or one section taken from a surgically removed specimen is not apt to tell you what the entire composition of the tumor is. It will tell you only what is present in that particular section. In our series of autopsy cases in which the tumors had not penetrated all the way through the muscularis of the bladder, we found there were ten papillary carcinomas, one of which had metastasized. There were four epidermoid carcinomas, and none had metastasized. There were no undifferentiated carcinomas in that group.

[Slide] In our large group in which all the tumors had passed completely through the muscularis of the bladder, we had twenty-eight papillary carcinomas, eleven of which had metastasized; thirty-five epidermoid carcinomas, of which twenty-two had metastasized; and eighteen undifferentiated carcinomas, of which fifteen had metastasized. The only reason I mention that is this: I think there are two points to be borne in mind. First, when the tumors have penetrated the bladder wall to approximately the same depth, the epidermoid carcinomas have metastasized a good deal more often than the papillary carcinomas at corresponding levels of cellular differentiation; and the undifferentiated carcinomas have metastasized more often than the epidermoids. Second, a section showing a well-differentiated carcinoma may prove misleading, because in another area of the same tumor undifferentiated carcinoma may exist.

Dr. William P. Herbst (Washington, D. C.): I would like to draw attention to Dr. Dean's presentation and comment on the fact that it was a very nice link in our chemical chain of information in malignancy. Looking toward the future, the chemical aspect of this problem is much more important than the cytology, and this glycerophosphatase estimation contributes in the enzyme aspect of our malignant problem.

Dr. Benjamin S. Barringer (New York, N. Y.): I would like to close on Dr. Patches' very nice presentation of mucinous adenocarcinoma of the bladder. The largest bladder carcinoma that I ever saw was a colloid carcinoma of the bladder reported, I think, in this Association a good many years ago. That tumor was as high as the umbilicus. It looked like a pregnancy. It was removed very nearly down to the trigone in toto.

I put a suprapubic tube in place and within three months the patient had reformed a fairly decent bladder, the wound had closed, and he could urinate very well, but a little more frequently than normal. Nearly three years later he died of an abdominal recurrence of his tumor.

DR. ARCHIE L. DEAN (New York, N. Y.): In commenting on Dr. Colby's splendid presentation and Dr. Jewett's discussion, I would say that we make cystoscopic biopsies to help in diagnosis and treatment, and I think there is no condition where we must know the true situation more accurately than when ureteral transplantation and cystectomy are considered.

We have studied the microscopic pathology of our patients quite seriously, and have been much disappointed to learn in a large proportion of our cases in which we had performed these formidable operations on patients whose specimens, removed through the cystoscope, showed grade 2 carcinoma, that the pathologist, after examing the entire bladder after removal, discovered that we were really dealing with cancers of grade 3, or even 4.

Therefore, while we are still groping for a true clinical classification of these tumors, we should realize the inadequacies of our recognized diagnostic methods.

DR. GEORGE R. LIVERMORE (Memphis, Tennessee): It is very gratifying to me to hear Dr. Colby tell us that he does a wide excision, introduces radium and later has the patient given deep x-ray, a method that I have used and advocated for years.

DR. FLETCHER H. COLBY (Boston, Massachusetts): I don't think you can depend entirely on biopsy. It has been fairly accurate in our hands. We grade these tumors according to the highest area of malignancy, so if in one part of the tumor we find cells of low malignancy and in another part cells of high malignancy, the tumor is graded according to the area of highest malignancy.

THE PRESENT PICTURE IN CHEMOTHERAPY IN PROSTATIC CARCINOMA

WILLIAM P. HERBST, M.D.
Washington, D. C.

The treatment of advanced carcinoma of the prostate gland by administration of steroid substances with so-called estrogenic properties, by removal of testicular tissue and by irradiation of the pituitary gland, the adrenal glands or the testicles and general pelvic area, has been under observation for more than five yeors.

The use of estradiol dipropionate and diethylstilbestrol in the treatment of seven patients with carcinoma of the prostate was first reported in March, 1941. Although all of these patients were in the advanced stages of the malignant process, the average survival period was thirty-seven months. This increased life expectancy was most pleasing and encouraging, as was the fact that the relief of pain, to varying degrees, was an outstanding incident in this series.

Irradiation of the pituitary gland in one patient has been reported.[4,10] Huggins[7] has reported the results of castration and the administration of estrogen or androgen on the serum phosphatase, in cases of advanced carcinoma of the prostate, as well as the results of removal of the adrenals. Since then many reports have appeared on the modification of the chemical soil of the body, from the point of view of rendering that soil unfavorable for the development of carcinoma of the prostate or for the development of other malignant processes.

The most comprehensive report of the comparison between treatment by castration and treatment by administration of stilbestrol has been furnished by Nesbit.[11] His report indicated that, insofar as studied, very little difference could be observed in the general course of the condition in these two groups of patients. Kearns,[8] in reporting his experience with the administration of estrogens in the treatment of patients with carcinoma of the prostate, advocated the use of estrogens as the sole form of treatment.

He also featured the utilization of the blood sedimentation rate as an index to the clinical course of the condition.

During the five-year observation period the following plan of treatment has been evolved. If obstruction and pain are not symptoms, inoperable cases of prostatic carcinoma are not treated. If, however, these symptoms are present, the obstruction is treated by resection, either transurethral or retrograde, depending on the technical factors involved, and the pain, whether it be local or metastatic, by castration (Chute technique). General supportive measures consisting of the administration of vitamins, when the tongue indicates deficiency, and the use of hematinics and transfusions, when the blood picture is unsatisfactory, are also carried out. Chemotherapy, instituted for the purpose of combatting the infection that is sometimes present, has been found to assist materially in the reduction of pain in many instances. When the time comes, following castration, that pain is no longer controlled, estrogenic substances, consisting of stilbestrol, estradiol dipropionate and ethinyl estradiol, are administered in the smallest effective dose, according to the need of each case, and then in increasing amounts as indicated by the patient's condition. In not a single instance has this subsequent use of the estrogenic steroids failed to be effective if the castration was effective in the first place. This observation, however, does not agree with the observation of Higgins[6] and Huggins. Additional control of pain has been obtained by irradiation of the pituitary gland (1,500 r on both sides) in three out of five cases. Pain in the areas involved by metastases has been relieved by irradiation (small doses) employed on a symptomatic basis. The relief of pain has also been accomplished by the spinal injection of ammonium chloride. Opiates are relied on in the terminal stage of the disease.

In a few instances castration and the administration of estrogens have not only failed to be inhibitory but on the contrary have appeared to stimulate a rapid extension and dissemination of the malignant process. This unfortunate situation existed even though the patient seemed to be improving generally. Phosphatase estimations have been paradoxical in these cases.

A vasomotor instability which developed in one patient following castration was not controlled by the administration of estrogens and when, eventually, androgens were administered, they were equally

ineffective. Benzedrine has been reported to be effective for the control of this phenomenon. In three instances, a petechial syndrome developed following the administration of the steroids but this complication was controlled satisfactorily by the administration of calcium gluconate by mouth or by injection. There is a suggested association between the administration of these estrogenic steroids and the development of cerebral hemorrhage. Nesbit and I both have observed this phenomenon. However, Nesbit does not believe that there is any relationship between cause and effect.

The deposit of fat in the pubic area is a striking characteristic in those patients who have received prolonged steroid therapy. Priapism has been restored following castration and some of these patients have subsequently presented themselves for the treatment of gonorrhea. Breasts, typical of female breasts, have developed following the administration of estrogens over long periods of time.[3] In cases in which this breast development has been painful, the breasts have been amputated. This surgical measure renders practicable an effective dosage of the steroids.

Carcinoma of the male breast has been beneficially influenced by castration.[1] In cases of female breast metastases, the administration of testosterone has produced favorable results. One case of osteosarcoma, in a female, was benefited strikingly by the administration of large doses of stilbestrol in conjunction with deep x-ray therapy.[2] Cases of testicular malignancy metastases have been helped by castration.[5,9] In one patient a severe degree of diabetes was remarkably improved by castration and the improvement continued when estrogens were subsequently administered for further control.

All types of metastases have been observed and in none is there a typical pattern. Both osteoblastic and osteoclastic lesions have been seen. Occasionally both types of lesions have been found in the same person, but ordinarily only a single type of lesion has been found. Post-mortem examination of the pituitary glands of three patients revealed no cytological abnormalities.

The adrenals have not been found to be of any value in indicating the severity of the malignant process. The results of studies in the ketosteroids have not been found to be reliable indicators of the clinical course of the malignancy.

Steroid metabolism appears to be a vital problem in the clinical

course of malignancy. Many steroids are variably changed following their administration; i.e., estrogens may lose their estrogenic properties through the metabolic processes. The liver metabolizes the natural estrogens with greater facility than it does stilbestrol. Cholesterol and various steroid substances involve the liver and the adrenals to a great extent. The influence of vitamins and enzymes and the role lipides play also focus attention on the liver. These observations are not only interesting but also significant because they emphasize the great need for a more comprehensive knowledge of liver chemistry, which, if we possessed it, would probably shed light on those chemical problems which may prove to be the key to an understanding of malignant tissue metabolism control.

Remarkably enough our experience with the use of castration in cases of extensive carcinoma of the prostate gland seems to be more or less parallel to the experience of the British, in the latter part of the last century, with their use of bilateral oophorectomy in cases of inoperable carcinoma of the breast.

Despite that fact that all of the first seven cases of advanced carcinoma of the prostate, treated with steroid substances, have died, encouragement is justified because of the increase in life expectancy and the reduction of pain, to varying degrees, in these patients. The most encouraging aspect of our present position in the treatment of prostatic malignancy is found in the fact that we have a large store of chemical data which should be helpful in pointing the way to the eventual chemical control of cancer, not only of the prostate gland but of other organs as well.

SUMMARY

The results of the administration of steroid substances to patients with advanced carcinoma of the prostate gland are reviewed.

The plan for treatment of patients with prostatic carcinoma is discussed.

A more comprehensive knowledge of liver chemistry is urged in order to be able to attack more easily the chemical problems which probably hold the key to an understanding of malignant tissue metabolism control.

The great amount of chemical data we have accumulated should be an aid in obtaining chemical control of cancer.

1801 Eye Street, N.W., Washington, D. C.

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ENDOCRINE THERAPY IN CARCINOMA OF THE PROSTATE: PREPARATION OF PATIENTS FOR RADICAL PERINEAL PROSTATECTOMY

J. A. CAMPBELL COLSTON, M.D., and HERBERT BRENDLER, M.D.

From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland

As soon as the efficacy of the endocrine management of carcinoma of the prostate, whether by orchidectomy, the administration of estrogens, or a combination of both, had been established by numerous observers, chiefly through the fundamental investigations of Herbst[5] and of Huggins,[6,7] carefully compiled studies soon became available concerning the extent of regression of the primary neoplasm and its metastases following the various types of therapy. From extensive reviews of statistics, as well as from experience gained in treating 200 patients with prostatic cancer at the Brady Urological Institute by the administration of stilbestrol, we have come to expect objective regression of the primary growth in approximately 75 per cent of the cases, and of its metastases in approximately 45 per cent.

In our clinic we have found it advantageous to classify cases of prostatic carcinoma into four main groups:

I. Early: in which the malignant process is confined to the gland itself, and is therefore admirably suited for radical extirpation.

II. Moderately advanced: in which the growth has spread into the bases of the seminal vesicles, or into the apex of the gland, or both.

III. Advanced: in which, on initial examination, there exists obvious extension throughout the region of the seminal vesicles, infero-lateral ligaments, membranous urethra, and with fixation of the outer layers of the rectum.

IV. Metastatic: Metastases may occur in all three of the above groups, but are, of course, most commonly seen in Group III.

During the past three years we have encountered a number of cases in Group II which have responded so satisfactorily to stilbestrol therapy that radical surgery subsequently has been under-

taken, in order to afford the patients the chance of a complete cure. It is with the management of these cases which may properly be classified as moderately advanced that this paper is primarily concerned.

THE ACTION OF STILBESTROL

The mode of action of the endocrines in prostatic cancer is not yet completely understood, nor has the question of stilbestrol therapy versus castration been settled. It is apparent, however, that the actively growing malignant cells require androgen for their viability, and when it is denied them, as after orchidectomy, or when it is neutralized, as seems to occur after the administration of stilbestrol, these cells undergo certain changes which can be demonstrated histologically and chemically. As Huggins has stated: "Androgen control seriously disturbs the enzyme mosaic of the cancer cells, at least with respect to the important energy-producing protein-catalysts, the phosphatases. As a contribution to the general problem of cancer treatment, it is well to emphasize that any interference with an important enzyme system of a cell, normal or malignant, will cause in that cell a decrease of size and function."[7]

The cytologic changes in the cancer cells following stilbestrol therapy have been intensively studied by Kahle, and others.[8,11] These observers were able to demonstrate definite regressive changes in the nuclear and cytoplasmic material. These changes consist at first of pyknosis of the nuclei and vacuolization of the cytoplasm. Later there occur progressive fragmentation and disappearance of nuclear material, rupture of cell membranes, loss of cellular outline, and finally, replacement by fibrous stroma, smooth muscle, and round cells.

The fact that recrudescence usually occurs after varying lengths of time has been adduced by most observers as evidence that the cancer cells are not actually destroyed, but simply remain dormant until becoming reactivated (Barringer.)[1] However, it is common clinically to note that, despite extensive and progressing metastatic manifestations elsewhere during the administration of stilbestrol, the prostate itself remains soft, even atrophic, and in many instances the diagnosis of carcinoma cannot be made by subsequent rectal palpation. Moreover, from a histological standpoint, as

shown by Kahle and others, it would seem that actual cell death has occurred following stilbestrol therapy.[8,11]

Clinically, after the administration of estrogens, one notes in about 75 per cent of the cases a generalized softening of the primary neoplasm, associated with shrinkage in size. These changes are variable, and this variability may be related to the histologic pattern of the tumor, as has been suggested by some, or to the total dosage of estrogen employed. In those patients, in whom the carcinoma by rectal palpation is classified as moderately advanced (Group II), we have gained the impression from serial examinations during stilbestrol treatment, that the earliest signs of regression appear in the periphery of the growth. This has led to the supposition that possibly the marginal cells are more actively growing, and therefore show the effects of androgen deprivation more acutely than do those located nearer the center.

Whatever the explanation, the clinical observation has been that, under the influence of stilbestrol, the cancerous process first seems to recede out of the bases of the seminal vesicles and apex of the prostate. This observation has been responsible for our feeling that patients with what has hitherto been considered inoperable prostatic cancer, can be given the possible opportunity of cure by radical surgical excision following adequate estrogenic preparation.

THE RADICAL OPERATION

From the insidious nature of the growth of carcinoma of the prostate, it is obvious that early diagnosis is extremely difficult, and in the majority of cases, when the diagnosis is first made, the primary neoplasm has extended beyond the capsule into the contiguous structures. The actual percentage of cases deemed suitable for radical surgical removal varies in different clinics. Prince and Vest performed the operation on 9 per cent of patients with prostatic cancer examined at the University of Virginia in a period of two years.[10] In an earlier study it was found that 22.7 per cent of all cases admitted to the Brady Urological Institute between 1937 and 1942, with a diagnosis of carcinoma of the prostate, were subjected to radical surgery.[2] The latter percentage is higher than ordinarily would be expected because numerous patients in whom a diagnosis of early carcinoma had been made elsewhere, were referred to this clinic in the hope that they could be cured by the

radical operation. However small the actual figure, it must be borne in mind that those patients who fulfill the conditions for radical extirpation must not be denied the chance of cure by this method.

It is well to review the clinical criteria for radical surgery in carcinoma of the prostate:

1. On rectal palpation the growth must not extend beyond the capsule, into the bases of the seminal vesicles, or into the region of the membranous urethra. The gland must be freely movable since fixation indicates spread into the periprostatic tissues.

2. No demonstrable metastases must be present. Acid phosphatase estimates are helpful in many cases, but often may remain at normal levels in the presence of extensive metastatic lesions.

3. The patient must be a good surgical risk, and his life expectancy should be reasonable. It is doubtful whether patients in the eighth or ninth decades should be submitted to the operation, especially in view of the essentially slow-growing characteristics of the tumor in these older individuals.

RESULTS

The postoperative results of the radical operation at the Brady Urological Institute have been reviewed in detail in earlier publications.[3,13] It has been pointed out that the operative mortality ranges between 5 and 6 per cent, a figure which compares very favorably with the results of surgery performed for the cure of cancer elsewhere in the body. In the last series of cases reported, there occurred four hospital deaths in a total of seventy-three radical prostatectomies done from 1937 to 1942, a mortality percentage of 5.5. Since 1942 there has been only one death directly attributable to operation. There are several reasons for the progressive reduction in mortality since 1904, when Young performed the first radical perineal prostatectomy for cancer. These include better methods of hemostasis, including the liberal use of blood transfusions, as well as chemotherapy and the antibiotics. The use of spinal anesthesia has provided better relaxation of the perineal musculature, thus materially improving the technique and shortening the duration of the operation.

THE PREOPERATIVE ADMINISTRATION OF STILBESTROL

The preparation of patients for radical perineal prostatectomy by

the use of stilbestrol has been recommended before,[4,9] and Vallett has reported a case where the radical operation was successfully performed after castration.[12] Hitherto, however, no reports have appeared in the literature where a series of cases so managed has been carefully followed and studied from that standpoint. At the Brady Urological Institute 200 cases of cancer of the prostate have been treated with stilbestrol, in all of which the primary neoplasm was considered too extensive on first examination to justify radical extirpation. The seven cases reported here were classified as moderately advanced on rectal examination. All were then maintained on stilbestrol therapy for varying periods, during which time serial rectal examinations were performed. The response of each of these patients to the administration of estrogen was so gratifying that it was deemed worthwhile to perform the radical operation in order to attempt a complete eradication of the disease. In several other patients similar regression occurred, but their general physical condition and life expectancy contraindicated extensive radical procedures.

In the seven cases submitted to radical prostatectomy, the preoperative dosage of stilbestrol was 1 to 2 mg. per day. No essential difference in the rapidity or degree of regression in the dosage recommended has been noted with larger doses. The use of stilbestrol in the dosage recommended has not been attended by untoward symptoms, save for slight swelling and tenderness of the nipples, and inasmuch as the growth has receded very satisfactorily on this dosage, larger amounts have not been employed.

CASE REPORTS

Case 1.—BUI 34370, J. E. A., a sixty-eight year old white man, was first examined November 9, 1943. Symptoms consisted of increased urinary difficulty, moderate frequency, and nocturia one to four times, of one year's duration. He gave no history of back or perineal pain, or apparent weight loss. He had been examined elsewhere six weeks previously, at which time a small, hard, oval nodule had been discovered in the right lobe of the prostate. He had therefore been referred here for possible radical perineal prostatectomy. Physical examination revealed the patient to be in good condition. The penis showed moderately advanced Peyronie's disease. Scrotal contents were normal. On rectal examination the prostate was slightly broader than normal. Both lateral lobes were irregular and contained areas of stony hard induration, more pronounced on the right. There was evidence of extension to the apex of the prostate and region of the membranous

urethra. Both seminal vesicles were palpable, but not indurated (Fig. 1, *A*). There was no x-ray evidence of bony metastasis. The acid phosphatase was normal.

Because of extension of the disease towards the apex, the case was considered unfavorable for radical cure at that time. Therefore the patient was begun on stilbestrol, 1 mg. per day, and maintained on

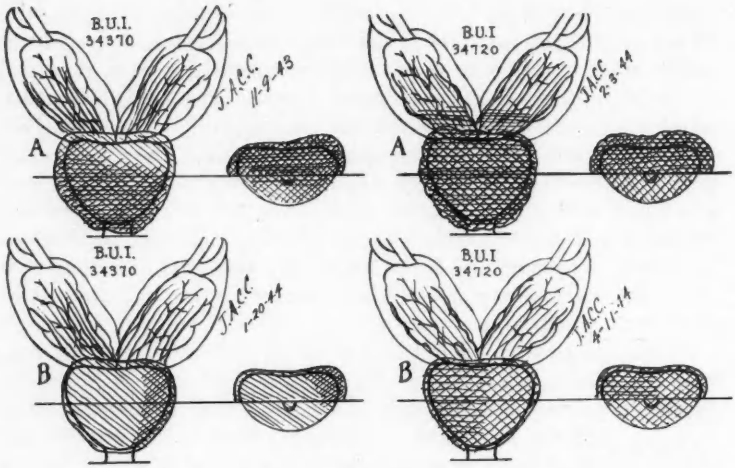


Fig. 1. *(left)* Case 1. (*A*) Diagrammatic representation of rectal findings on initial examination. (*B*) Ten weeks after institution of stilbestrol.
Fig. 2. *(right)* Case 2. (*A*) Diagrammatic representation of rectal findings on initial examination. (*B*) Ten weeks after institution of stilbestrol.

this regime for almost seven months. During this time serial rectal examinations showed progressive shrinkage and softening of the neoplasm (Fig. 1, *B*).

On May 27, 1944, the patient was readmitted and prepared for operation. Laboratory studies showed: hemoglobin, 96; white blood cells, 6,100; phthalein excretion, 65 per cent in two hours. The urine was negative except for an occasional white blood cell; culture was sterile.

On May 29 radical perineal prostatectomy was carried out and followed by an uneventful convalescence.

Pathological studies showed adenocarcinoma of the prostate and involvement of the bases of both seminal vesicles.

The patient was discharged from the hospital on the twenty-ninth postoperative day, voiding a good stream with perfect control. On the last visit, one year after operation, the patient was found to be in

good general condition with no evidence of local recurrence or distant metastases. He was passing a stream of good calibre and force.

Case 2.—BUI 34720, K. H. B., a fifty-nine year old white man, was first seen February 3, 1944. He came here after a diagnosis of carcinoma of the prostate had been made elsewhere and orchidectomy advised. There was no history of urinary symptoms, weight loss or pain. Previous x-ray studies had been negative for metastases, and acid phosphatase was normal.

On examination the patient was found to be in good condition. The external genitalia were normal. The prostate was slightly broader than normal, fixed, irregular and stony hard throughout. There was evident extension into the apex as well as into the bases of both seminal vesicles (Fig. 2, *A*).

Radical extirpation was thought to be contraindicated at that time, and the patient was placed on stilbestrol, 2 mg. per day. This was maintained for approximately two months. During this time serial rectal examinations demonstrated such satisfactory regression of the carcinomatous process that it was thought advisable to carry out radical prostatectomy (Fig. 2, *B*). Laboratory studies showed: hemoglobin, 13.3 gm.; white blood cells, 5,600; blood urea, 20 mg.; phthalein excretion, 75 per cent in two hours. The urine was negative; culture negative.

On April 12, 1944, radical perineal prostatectomy was done. Convalescence was uneventful except for one febrile rise after passage of a sound. The patient was discharged twenty-three days after operation, voiding well and with good control.

Pathological sections showed extensive adenocarcinoma of the prostate with involvement of the bases of both seminal vesicles.

Four days after leaving the hospital the patient had acute urinary retention and was treated elsewhere for a stricture at the site of anastomosis. A suprapubic cystostomy was done, and a urethral catheter left in place. The tube was removed five days later, and the patient was able to void satisfactorily. At the present time the void stream is free and urinary control satisfactory. The patient has now resumed full activity. He frequently plays eighteen holes of golf a day, and experiences no urinary leakage whatever. However, at the end of an especially strenuous day, the patient occasionally notices slight dribbling.

Case 3.—BUI 34757, Dr. W. N. F., a sixty-one year old white physician, was first examined at the Brady Urological Institute on February 11, 1944. In the course of a general physical examination elsewhere, the prostate was noted to be hard and irregular. The patient was followed periodically for several months. A bilateral orchiectomy was advised, and on the suggestion of a colleague he came to the Brady Urological Institute. No nocturia was noticed at any time, and only slight hesitancy. There was no history of pain or weight loss. The patient had a long history of alcohol addiction.

On general physical examination the patient was in good condition. The external genitalia were normal. There was a small, reducible hernia present at the right external ring. Rectal palpation showed the prostate to be moderately broader than normal. It was irregular, indurated and stony hard throughout. The right lobe was especially prominent. The induration had extended into the apex of the prostate

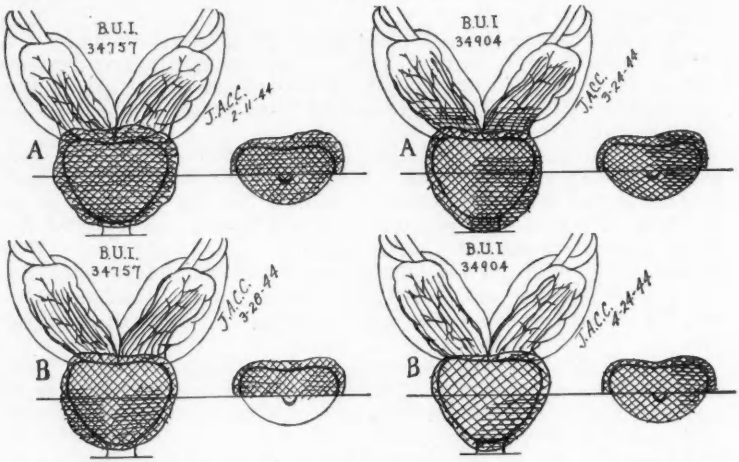


Fig. 3. *(left)* Case 3. (*A*) Diagrammatic representation of rectal findings on initial examination. (*B*) Six weeks after institution of stilbestrol.
Fig. 4. *(right)* Case 4. (*A*) Diagrammatic representation of rectal findings on initial examination. (*B*) Four weeks after institution of stilbestrol.

and up into the bases of both seminal vesicles (Fig. 3, *A*). There was no x-ray evidence of metastases. Acid phosphatase studies were normal.

Although the growth had not spread beyond the confines of the capsule, it was thought to be too extensive at that time to insure a complete cure by radical operation. For this reason stilbestrol, 2 mg. a day, was advised. Rectal examination six weeks later revealed definite regression of the neoplasm both in size and degree of induration (Fig. 3, *B*).

The patient was readmitted March 28, 1944, and prepared for radical operation. Laboratory studies revealed: hemoglobin, 12 gm.; white blood cells, 5,200; blood urea, 20 mg. per cent; phthalein excretion, 82 per cent in two hours. Urine was negative; cultures sterile.

On April 1, 1944, a radical perineal prostatectomy was carried out, followed by a completely uneventful convalescence except for slight

leakage after removal of the urethral catheter on the fourteenth postoperative day. The patient left the hospital nineteen days after operation, voiding well and with good control.

Pathological studies showed extensive adenocarcinoma of the prostate, involving the bases of both seminal vesicles.

Two months later symptoms of urinary difficulty developed, and he required several efforts to empty his bladder. Urinary control, however, was excellent.

He was re-examined on July 11, 1944. No evidence of local recurrence or distant metastasis was found. However, a stricture had developed at the site of the anastomosis. The residual urine was 30 c.c. The patient therefore was readmitted to the hospital and the stricture dilated under spinal anesthesia. He was discharged after several days, voiding an excellent stream and with normal control.

Case 4.—BUI 34904, C. E. H., a sixty year old white man, was first examined at the Brady Urological Institute on March 24, 1944. He was referred by his physician who had followed him for about one year because of increased urinary difficulty and hesitancy as well as an enlarged, rather hard prostate. There had been no history of back or perineal pain, and no weight loss.

On physical examination the patient seemed to be in good general condition. The external genitalia were normal. On rectal examination the prostate was moderately broader than normal, and especially prominent on the right side. The right lobe was of stony hard induration, especially towards its outer edge and well down toward the apex. The left lobe was firm, but not of third degree. The seminal vesicles were thickened but not involved. The growth had apparently extended beyond the capsule on the right side, and particularly into the membranous urethra (Fig. 4, *A*). Residual urine was 85 c.c. There was no x-ray evidence of metastases.

Radical operation was thought to be unjustified because of the extent of the malignant process. The patient therefore was started on stilbestrol, 1 mg. per day. He was seen again one month later, at which time he was voiding with considerably less difficulty. Definite regression of the neoplasm had occurred. Stilbestrol was continued another month, and at the end of that time, on rectal examination, it was difficult to detect any areas of stony hardness or make a gross diagnosis of carcinoma (Fig. 4, *B*).

The patient was readmitted May 23, 1944, and prepared for radical perineal prostatectomy. Laboratory studies disclosed: hemoglobin, 100; white blood cells, 8,500; blood urea, 28 mg. per cent; phthalein excretion, 85 per cent in two hours. Urine contained a trace of albumin and 4 to 5 white blood cells.

On May 24 radical perineal prostatectomy was carried out and followed by an uneventful convalescence. The urethral catheter was removed the fourteenth postoperative day. The patient voided an excellent stream, and remained dry perineally.

Pathological studies showed carcinoma of the prostate not involving the seminal vesicles. It was predominantly adenocarcinoma in type, with a multiplicity of form, and showing stilbestrol changes.

The patient was discharged nineteen days after operation, voiding well and with good control.

After returning home he did well for about fourteen months. At that time he noticed some diminution in the size and force of the stream. He was re-examined September 6, 1945, and found to be in excellent general condition. There was no evidence of local return of the cancer or distant metastases. A soft stricture at the site of the anastomosis was easily dilated, following which the patient developed acute retention. He was hospitalized twenty-four hours and discharged voiding easily with normal control.

Case 5.—BUI 36309, M. W., a white man aged sixty-eight, was first examined at the Brady Urological Institute on February 27, 1945 For the preceding year he had suffered from vague gastrointestinal symptoms manifested chiefly by gaseous distention. His local physician had discovered a suspicious nodule in the prostate and referred him to a urologist who diagnosed carcinoma of the prostate, but considered the process too extensive for radical operation. The patient was referred to this clinic. He had no history of any urinary symptoms whatsoever. Rectal examination disclosed the prostate to be considerably broader than normal. The left lobe was nodular and of stony hard induration, and there was nodularity of the right lobe which also was stony hard, but not quite so prominent as the left. The bases of both seminal vesicles were invaded, particularly on the left (Fig. 5, *A*). There was no x-ray evidence of bony metastases. The serum acid phosphatase studies were normal.

The initial impression was that the growth was too extensive for radical operation. Stilbestrol, 1 mg. a day, was started. When seen six months later, a most remarkable change in the palpatory findings had occurred. The gland was only slightly broader and more prominent than normal. No nodules were present, and the elevation on the left side had disappeared. The entire gland was elastic and compressible, and not adherent. The vesicles and the base of the bladder above the gland were quite soft (Fig. 5, *B*). Another x-ray again demonstrated no evidence of metastases.

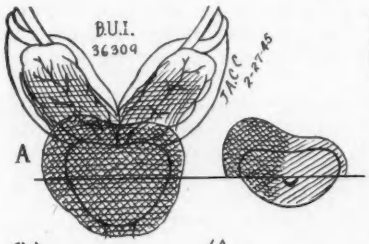
The patient was readmitted on August 15, 1945, and prepared for radical perineal prostatectomy. All laboratory findings were negative.

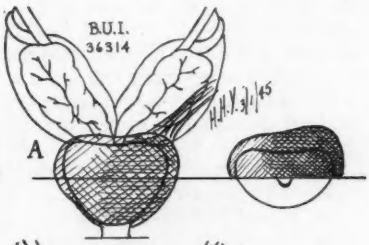
On August 17 radical perineal prostatectomy was performed. The convalescence was smooth. The urethral catheter was removed the eleventh postoperative day, following which all urine drained by way of the perineum until reinsertion of the catheter on the seventeenth postoperative day. The catheter was finally removed the twenty-second day, after which the perineum remained completely dry. For the first three days the patient was almost totally incontinent, but at the end of that time he regained control gradually so that when he was discharged

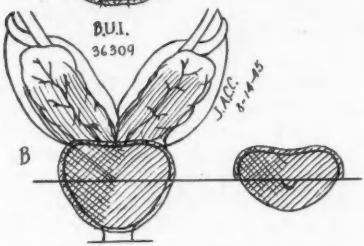
on the twenty-sixth postoperative day he was voiding a normal stream with excellent control.

Pathological studies showed adenocarcinoma of the prostate involving the bases of both vesicles, chiefly the left, with scattered areas of stilbestrol change.

The patient has not been seen since, but a letter from him one







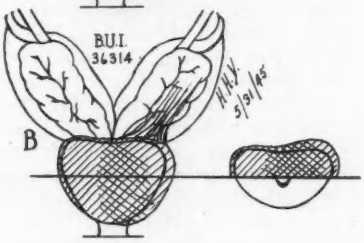


Fig. 5. *(left)* Case 5. (*A*) Diagrammatic representation of rectal findings on initial examination. (*B*) Six months after institution of stilbestrol.

Fig. 6. *(right)* Case 6. (*A*) Diagrammatic representation of rectal findings on initial examination. (*B*) Three months after institution of stilbestrol.

month after operation stated that he was in excellent health and voiding satisfactorily.

Case 6.—BUI 36314, E. R., a sixty-two year old white man, was first seen on March 1, 1945. He had a history of onset of urinary difficulty and frequency one year prior to the first examination. Six months before examination the patient had been seen elsewhere, and had been treated periodically by urethral sounds and posterior urethral irrigations.

The patient was in good general condition. The external genitalia were normal. On rectal examination there was evidence of third degree induration and nodularity throughout the prostate, but chiefly on the right side, with infiltration of the perirectal tissues over an area 1½ cm. in diameter on the right side. Except for this, the carcinomatous process seemed to be confined within the capsule of the prostate (Fig.

6, *A*). There was no x-ray evidence of metastases. No serum acid phosphatase studies were obtained. The patient was placed on stilbestrol, 2 mg. per day. On this medication he developed some tenderness and soreness of the nipples, but there was some lessening in frequency and nocturia. The stream was perhaps slightly better. He was again examined on May 31, 1945, at which time the prostate felt distinctly better. The left lobe was slightly larger than normal, smooth and elastic throughout, and of second degree induration. In the lower portion of the left seminal vesicle there was induration, but the remainder felt soft. The membranous urethra was uninvolved, and the rectal mucosa smooth (Fig. 6, *B*).

The patient was admitted to the hospital on June 2, 1945. General physical examination was essentially negative. Preoperative laboratory studies included: hemoglobin, 13.7 gm.; white blood cells, 13,550; blood urea, 20 mg. per cent; phthalein excretion, 75 per cent in two hours. Urine was negative.

On June 11 radical perineal prostatectomy was carried out. At operation there was obvious extension into the tip of the right seminal vesicle and laterally to the pelvic wall on the right side. After removal of the prostate and seminal vesicles, there apparently still remained some neoplastic tissue on the right side. Postoperatively the patient had a smooth convalescence. The urethral catheter was removed on the fourteenth postoperative day, following which the patient voided an excellent stream with good control. On the sixteenth postoperative day he suddenly developed a left hemiparesis which manifested itself as a seventh nerve palsy and marked motor loss of the left arm and leg. This cleared rapidly after about two weeks and was considered to have originated on an angiospastic basis. The patient was discharged on the thirty-fifth postoperative day, voiding satisfactorily with excellent urinary control.

Pathological studies showed adenocarcinoma of the prostate with marked anaplasia and with some diversity of the histologic pattern.

The patient was seen three weeks after leaving the hospital. A soft stricture at the site of the anastomosis was easily dilated. He was again seen after another three weeks' period and found to be voiding a good stream with normal control.

The patient died in May, 1946. His physician said that he could feel some evidence of malignancy on rectal examination.

Case 7.—BUI 37313, Dr. W. T. B., a seventy year old white physician, was admitted to the Brady Urological Institute October 3, 1945, complaining of nocturia and burning on urination for approximately three to four years. He had been referred by his own physician who had discovered a hard nodule in the prostate on rectal examination.

On physical examination the patient seemed to be in excellent general condition. The external genitalia were entirely normal. On rectal examination the prostate was somewhat broader than normal. Both lateral lobes were irregular and stony hard throughout with the in-

duration extending into both seminal vesicles, particularly on the left side (Fig. 7, *A*). Laboratory studies included: hemoglobin, 14 gm.; white blood cells, 9,600; blood urea, 20 mg.; phthalein excretion, 73 per cent in two hours. Urine contained 8 to 10 white blood cells per high power field; cultures were sterile. There was no x-ray evidence of bony metastases.

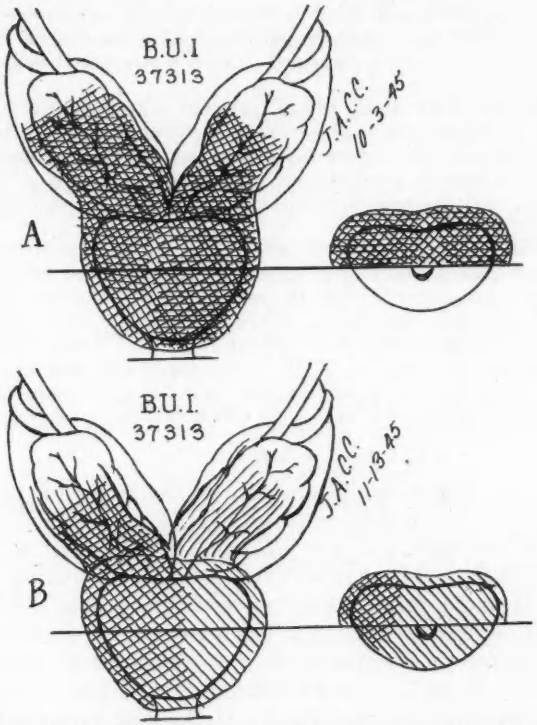


Fig. 7. Case 7. (*A*) Diagrammatic representation of rectal findings on initial examination. (*B*) Six weeks after institution of stilbestrol.

It was believed that although this could be classed as a moderately advanced carcinoma of the prostate which had extended into both seminal vesicles, the radical operation should be deferred in the hope that following a course of stilbestrol, the growth would regress sufficiently to permit an easier operative procedure and insure a better functional result. The patient was discharged and placed on stilbestrol, 2 mg. per day.

He was readmitted to the Brady Urological Institute for the second time on November 13, 1945. Rectal examination disclosed the prostate to be only slightly broader than normal. The right lobe was smooth and firm, but elastic and compressible throughout. The left lobe contained no evidence of stony hardness, and was also smooth and compressible (Fig. 7, *B*). There had been a very definite and gratifying response to stilbestrol therapy. It was decided that the patient was now suitable for a radical operation. Preliminary labortory studies included: hemoglobin, 14.2 mg.; white blood cells, 8,700; blood urea, 20 mg. per cent. The voided urine contained 4 to 6 white blood cells per high power field.

On November 14, 1945, radical perineal prostatectomy was carried out. The postoperative course was entirely uneventful. The urethral catheter was removed the twelveth postoperative day following which the patient voided a good stream with excellent control. The patient was discharged sixteen days after operation to be followed by his own physician.

Pathological studies showed adenocarcinoma of the prostate, fairly well differentiated, with involvement of both seminal vesicles.

Several weeks after leaving the hospital the patient developed acute retention, and was seen by an urologist elsewhere who, after several dilatations, performed a transurethral resection. Following this procedure the patient became totally incontinent, but this has gradually improved so that he now has no nocturnal leakage, but has to wear a clamp during his surgical activities, which he has resumed.

SUMMARY

Endocrine therapy in the treatment of carcinoma of the prostate, either by the administration of estrogen or by orchiectomy, or a combination of both, has been proven by many competent observers to have a definite and most valuable place in the treatment of carcinoma of the prostate. Regression of the primary growth, as measured by rectal examination, has been noted to occur in approximately 75 per cent of the cases, and regression of metastases in 45 per cent. It has been postulated that this inhibitive effect results from an interference with the enzyme balance by endocrine therapy, and probably this effect is more pronounced on the younger, actively growing cells of the tumor, which are more dependent on androgen for their metastases. In spite of the intensive laboratory studies and many clinical observations that have been made on endocrine therapy of carcinoma of the prostate, no case has yet been reported in which complete disappearance or clinical cure has been obtained by endocrine therapy alone. From the results of experimental laboratory work and clinical research, it would appear

at present that a permanent cure with endocrine therapy of carcinoma of the prostate cannot be obtained.

The regression of the prostatic growth which occurs in an appreciable percentage of cases under endocrine therapy has led us to follow a series of cases in which on first examination the growth was considered too far advanced for complete extirpation by radical operation. Seven such cases are presented with charts of the prostatic neoplasm before and after endocrine therapy. In these seven cases it was considered that the regression of the neoplasm as far as could be judged by rectal palpation had progressed to a sufficient degree to permit the radical operation which was successfully carried out in these cases. There has been no operative mortality in this series, but two patients have developed complications resulting from stricture formation at the site of the anastomosis. One patient has died of recurrence and metastases one year after operation.

The patients in this series have all been operated upon within the last two years so that the presentation is in no sense intended as a study of ultimate mortality.

It is our impression that endocrine therapy for the preparation of patients to undergo the radical operation is of the utmost value in that:

1. We have observed numerous cases of moderately advanced carcinoma of the prostate for which orchiectomy or transurethral resection has been advised in the belief that the disease was too far advanced for radical extirpation.

2. Regression of the growth, which usually occurs, materially facilitates the operative technique in moderately advanced cases.

3. It is our hope that five-year cures will be obtained in some of the cases in which on physical examination the observer's opinion was that the prognosis for radical cure was unfavorable.

In view of the regression of the primary growth which usually occurs in cancer of the prostate following endocrine therapy and which is attributed to death of at least some of the malignant cells, presumably at the periphery of the lesion, it would seem advisable to institute endocrine therapy in all cases of carcinoma of the prostate, even those which fulfill the criteria for the radical operation.

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PRIMARY TUBERCULOSIS OF THE PROSTATE

CASE REPORT

N. P. RATHBUN, M.D.

Brooklyn, New York

Primary or solitary tuberculosis of the prostate, as evidenced by the literature, is an extremely rare disease. In all of the cases reported, the diagnosis has been made from tissue removed at operation, or at autopsy. I have found no case reported in which a diagnosis has been established in any other way. It is quite possible that this lesion may occur more commonly than is indicated by the available literature, due either to incorrect interpretation of symptoms or physical findings, or to incomplete pathological investigation or operative or autopsy specimens.

It is, I believe, generally considered that tuberculosis anywhere in the genital or urinary systems, in the vast majority of cases, is secondary to tuberculosis in some other part of the body, such as the lungs, the tonsils, the cervical or bronchial glands or the bony skeleton. Lesions of this character that develop in the urinary tract are practically always primary in the kidney, whereas lesions in the genital tract are usually primary in the epididymis. It has been variously estimated by many observers that when taken as a group under the general heading of urogenital tuberculosis, the prostate is involved in about 70 per cent of the cases, so that tuberculosis of the prostate, as a secondary lesion, is fairly common. The prostatic lesion in these cases is practically always secondary to a lesion in some other part of the genito-urinary system. Such cases are frequently seen and are familiar to all of us.

Many of the so-called primary or solitary lesions reported, including my own case, are doubtless open to criticism. In fact it would seem impossible to prove that the disease was confined to the prostate without a complete and careful autopsy. Walker, in a very careful study of tuberculosis of the genito-urinary tract, found only three acceptable cases: one reported by Crandon in which a complete autopsy showed no tuberculosis in any other part of the body, and two others reported by Krzywik. Koll in 1915 reported a

case subjected to suprapubic prostatectomy with a diagnosis of hypertrophy, in which tuberculosis had not been suspected but was demonstrated in the operative specimen. The patient made a "slow but good recovery." Barney reported a case in 1923 upon whom he performed a two-stage prostatectomy. Tuberculosis had not been suspected until the laboratory reported tuberculosis in the specimen removed. This case, however, had some thickening in one epididymis which might or might not have been tuberculous.

Scott in an excellent paper (1924) reported seven cases from the literature, including those noted above, but believed that only four were authentic. He added a case of his own, a patient who died from complications following perineal prostatectomy. The prostate on section showed definite tuberculous lesions. A careful and complete autopsy was performed. There was no evidence of tuberculosis in any other part of the genito-urinary tract. There was slight fibrosis of both apices of the lungs, as well as thickening of the pleura over these regions but on microscopic study of these areas no remaining tuberculous tissue was discovered; "one enlarged, indurated peri-bronchial lymph gland, which on section showed a few small white spots, was found on the left side. On microscopic examination, several areas of fibrous tuberculous tissue within which there still lingered a few very definite giant cells were discovered." This might have been and probably was the primary source of infection. Sturm and Thompson (1945) reported the case of a man who died following a complicated operation on his biliary tract. He had never complained of any symptoms referable to his urinary tract. A complete autopsy was performed, including sections of the prostate gland. In one lobe of the prostate a tiny abscess was found in which tubercle bacilli were demonstrated. A very careful search failed to reveal tuberculosis in any other part of the body. This would appear to be an authentic case. Young in his textbook, reports only one case of "pure prostatic tuberculosis proven" from the Brady Urological Institute and this case was associated with hypertrophy and operated upon with this diagnosis. Herman states that primary tuberculosis of the prostate is very rare.

CASE REPORT

A man, aged fifty, admitted to The Brooklyn Hospital on October 2, 1944, had had the usual childhood diseases with no complications. Many years ago he had what was diagnosed as pleurisy. He was sick only

three days, made a good recovery and had no further symptoms referable to his respiratory organs. Six years before admission he had an attack of right renal colic, at which time he passed a small calculus. He had no other symptoms referable to the genito-urinary organs until his present illness.

Five days before admission he had a severe chill followed by a temperature of 104° F. and associated with a dull pain in his upper right quadrant, referable to his right shoulder and radiating down his right arm. There was also a mild dysuria; examination of the urine showed marked pyuria. He was seen at his home by his family physician who prescribed sulfathiazole. His temperature subsided to normal promptly, as did the pyuria, but some pain and tenderness referable to both upper quadrants persisted and he was sent to the hospital for further study. Physical examination showed the following points of interest: he did not appear acutely ill; he was voiding urine at normal intervals with no discomfort, and an examination of the urine showed no abnormal elements. There was some tenderness over the gall bladder area and also in the left costo-vertebral angle. There was also tenderness on deep pressure over the lower dorsal and lumbar spine. There was a loud systolic murmur over the apex of the heart; the lungs were clear; pulse and temperature were normal; hemoglobin was 80 per cent and the red blood cells, 4,080,000; the white cell count showed 12,800 with polymorphonuclears 75 per cent; the blood chemistry was normal. His spinal fluid was under normal pressure and showed no abnormalities. The scrotum and its content were entirely normal. The prostate on rectal examination was slightly enlarged, smooth, soft and regular and not tender. Cystoscopy on October 5, 1944, disclosed slight general prostatic enlargement which did not appear to be obstructive; the bladder was normal and showed no trabeculations; the ureters were easily catheterized to the kidney pelves. All the specimens of urine were free from abnormal elements and were sterile on culture. (He had been taking sulfathiazole which may have had a bearing on this latter finding.) The phthalein excretion was normal and equal from both kidneys. X-ray studies, including bilateral pyelograms, showed normal kidney pelves and ureteral outlines; it did show, however, three small opacities in the abdomen which were interpreted as calcified mesenteric nodes and also evidences of a hypertrophic osteo-arthritis involving the lower dorsal and lumbar spine. He was discharged the following day practically free from symptoms, except for vague pains in both lumbar regions which were attributed to his osteo-arthritis.

He returned to business and remained well until October 17, eleven days after his discharge from the hospital. At this time he contracted a respiratory infection with a temperature of 103° and associated with marked dysuria. I saw him then at his home. The prostate was markedly enlarged, not fluctuant but exquisitely tender; I assumed that he had an acute prostatitis secondary to his respiratory infection and advised sulfathiazole and hot sitz baths. The temperature and respiratory

infection promptly subsided, but the dysuria became progressively worse amounting to practically complete retention, and required frequent catheterization.

He was readmitted to the hospital October 26 1944, in complete retention. His temperature was 99°. His white cell count showed a leukocytosis of 12,000 with polymorphonuclears, 75 per cent. The urine showed a moderate number of pus cells. (Unfortunately it was not cultured or stained for tubercle bacilli at this time.) The prostate was still large and tender but not fluctuant. An inlying catheter was placed in the bladder and sulfathiazole and hot sitz baths were continued. At the end of a week of catheter drainage, the prostate appeared slightly smaller and slightly less tender. The inlying catheter was removed and he was given an opportunity to void, but was unable to do so and the catheter was replaced. The condition of the prostate, as evidenced by rectal examination, was about the same. On November 8, 1944, a suprapublic cystostomy and bilateral vasectomy were performed. The bladder wall was slightly thickened and there was a marked intravesical protrusion of the prostate which, according to my operative notes appeared "more inflammatory than hypertrophic." His convalescence was uneventful; from time to time the suprapubic tube was clamped and he was urged to try voiding but again was unable to do so.

On November 24, 1944, after sixteen days of suprapubic drainage, a partial suprapubic prostatectomy was performed. It was noted that there was no clear line of cleavage; however, several pieces of prostate, aggregating about 40 gm., were enucleated and the procedure appeared to stablish a reasonably satisfactory channel. In the course of the enucleation I broke into a very small cavity containing a small amount of grumous material. Unfortunately no smears or cultures were made. Surprisingly enough, in view of the pathological findings reported later, he made an uneventful convalescence and was discharged on December 12, 1944, eighteen days after the second operation. The wound was entirely healed, and he voided freely at reasonably normal intervals.

A recent x-ray of the chest showed what was interpreted as fibrosis of the apex of the left lung. This might represent the scar of an old tuberculous lesion.

Pathological report (J. Arnold de Veer, M.D.): The specimen consisted of a number of prostatic fragments totaling about 40 gm. in weight. It included some friable, opaque material suggesting either inflammatory or neoplastic tissue.

Microscopic examination from many representative areas revealed widespread tuberculosis as well as evidence of hyperplasia. Extensive patches of caseation necrosis were bordered by epitheloid cells, including many Langhans cells. Small discrete tubercles with and without caseation necrosis were also numerous and widely distributed throughout the prostatic tissue. There were intervening areas of recognizable prostatic glandular structures, but the stroma was heavily infiltrated with lymphocytic plasma cells and large mononuclear phagocytic cells.

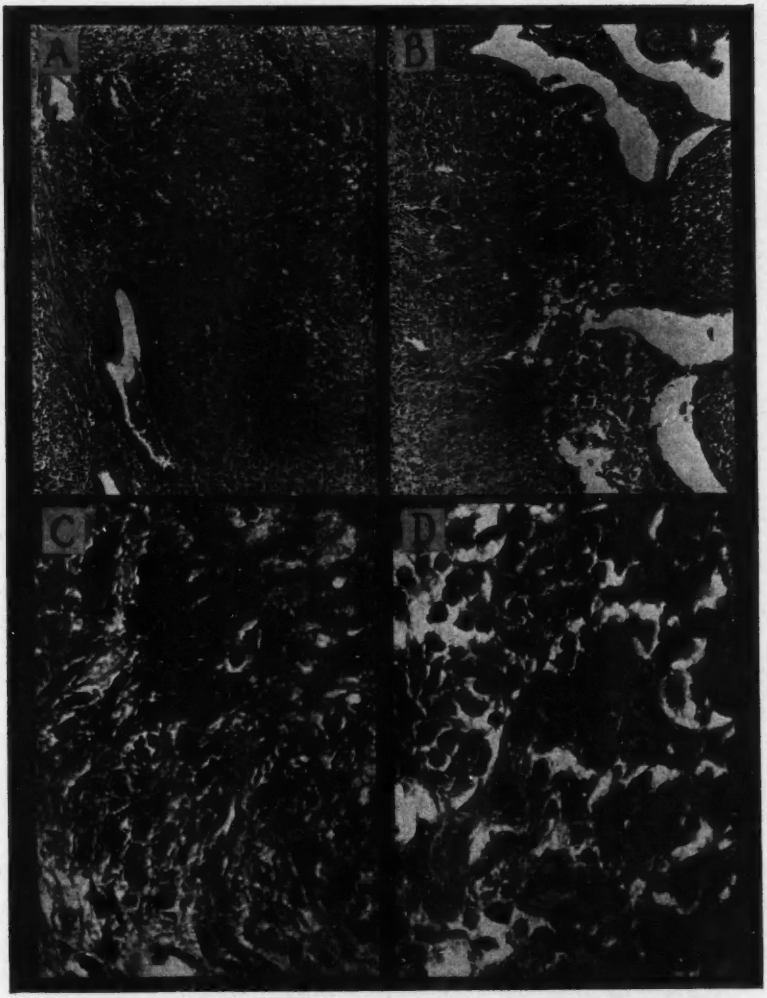

Fig. 1. Areas showing productive and exudative features of tuberculosis of prostate. In *A* there is an area of caseous necrosis in upper right corner with an area of epithelioid tissue bordering it. Remains of prostatic acini, surrounded by cellular infiltration occupy upper right of field. *B* includes a cluster of Langhan's giant cells. (*C*) Areas of epithelioid reaction shown in higher magnification than in *A* and *B*. *D* is from within an acinus and shows large mononuclear phagocytic cells as well as epithelioid derivatives of these cells in histoid arrangement; in other words, early tubercle formation within an acinus.

A noteworthy feature was the presence of large mononuclear wandering cells within the acini and, in many fields, these cells were assuming histoid structure suggesting early tubercle formation within the gland lumina. The entire picture was that of an active, acute and chronic tuberculosis in a prostate that had been the seat of hyperplastic changes. There was an absence of any fibrous encapsulation, indicating that the process was of relatively recent development. The acute, exudative features were predominant and may have been entirely attributable to the tuberculosis, although superimposed infection cannot be excluded. No suppuration was found (Fig. 1).

In view of those findings, I naturally believed that the prognosis was extremely unfavorable and that we might reasonably expect tuberculous manifestations in some other part of the body and, if he lived long enough, a tuberculous stricture at his bladder neck. However, he continues in excellent health. He reports from time to time at my office, the last time March 11, 1946. He has gained weight, he voids once at night; he passes clear urine in a forceful stream, he empties his bladder completely and a 25 F. sound passes easily. The long-time outlook is still uncertain and it is quite probable that he may eventually develop a stricture at his bladder neck.

DISCUSSION

There can be no question about the presence of an early active tuberculous infection in the prostate, and inasmuch as a careful investigation of the genito-urinary tract revealed no evidence of any similar lesion, it seems fair to assume that so far as that system is concerned it was primary.

It has not been proven that the lesion demonstrated in the prostate was a solitary one. However, a very careful history and physical examination failed to reveal any positive evidence of tuberculosis in any other part of the body, unless we consider his rather vague history of pleurisy many years ago as having been tuberculous, plus the finding of calcified mesenteric nodes in an x-ray and the recent radiogram of his chest, which might indicate a healed tuberculosis of the left lung. Not only was tuberculosis demonstrated in the prostate but it was of an acute fulminating type which corresponds in a way with the clinical picture. In this respect, the case presented would appear to be unusual, perhaps unique. It is interesting to speculate on the course of events in this particular case. One thought which has occurred to me is that his acute respiratory infection activated an unrecognized latent infection in a peri-bronchial gland with a resulting shower of tubercle bacilli in the blood stream which landed in his prostate.

SUMMARY

A case of acute prostatic tuberculosis engrafted upon an early hypertrophy is reported. A careful survey showed no evidence of tuberculosis in any other part of the body; it is of course a fact that certain findings would suggest the possible presence of a healed tuberculosis in the chest, which may have been latent and which was activated by an acute respiratory infection.

80 Hanson Place, Brooklyn, N. Y.

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DISCUSSION

DR. GEORGE G. SMITH (Brookline, Massachusetts): In regard to the very interesting paper of Dr. Colston, it would seem that there must be a wealth of pathological material which was gained from these prostates that were removed, and if Dr. Colston would give us just a brief word about that, I think it would be very interesting.

DR. J. DELLINGER BARNEY (Boston, Massachusetts): I thought in view of Dr. Rathbun's interesting paper, it might be well to mention the case of tuberculosis of the prostate which I reported in 1923. I did not suspect from the fact that the patient had just an ordinary chain of symptoms of the adenomatous prostate that there was tuberculosis, but the pathologist found tuberculosis in this adenoma which I removed. Subsequently, I examined the man most carefully in every way to see what evidences there were of tuberculosis, but could find none. I have seen the patient from time to time since that operation and have followed him pretty carefully. Up to date, we haven't had an autopsy, but he has had absolutely no clinical evidences of tuberculosis in any part of his body. He is in perfect health. He has no stricture of his urethra, and his bladder is functioning very normally, so perhaps it was a primary lesion and perhaps I did a very radical job when I took out his prostate.

DR. GEORGE R. LIVERMORE (Memphis, Tennessee): I would like to ask Dr. Herbst a question. In a report on his work two years ago he suggested that we increase the dosage of stilbesterol to 5 milligrams. Now after castration he advises small doses. I disagree with him in regard to castration. I prefer to use stilbestrol first and then if we do not get results we advise castration. If this fails, then more stilbestrol is given. I wish he would tell us more about his treatment of these cases.

DR. EDWARD L. KEYES (New York, N. Y.): I no more believe there is tuberculosis primary in the prostate than Dr. Rathbun does. I reported such a case many years ago, and arise merely to report

that the man is still alive and apparently well and has had no further clinical manifestation of tuberculosis. He spends his winters in Colorado.

These three cases reported here this morning support the impression that tuberculosis of the prostate is controllable by good surgery.

DR. WILLIAM P. HERBST (Washington, D. C.): In answer to Dr. Livermore, the dosage of estrogen, I think, is rather an interesting problem, and our feeling in regard to the estrogen is this: The body resents imbalances, and whether you remove the testicle or whether you administer steroid estrogenic-like substances, the body has a potential ability to adjust these imbalances.

We feel that when you take the testicular tissue out, that you produce a certain degree of imbalance. Interestingly enough, occasionally a rather old patient, say in his seventies or eighties, seemed to get a more prolonged satisfactory response than a younger individual, which may be interpreted possibly as showing the inability of that individual to adjust to the same degree as a younger individual, so that we have that feeling, and for that reason we feel that the smaller amounts of estogen administered will prolong the expectancy.

Insofar as dosage is concerned, we emphasize the smallest possible effective dose for that reason. The largest dose we have used is about 30 milligrams a day, 10 milligrams given three times a day orally. We also use it by injection, and according to studies that have been done an liver metabolism, we know that the liver will definitely metabolize these estrogenic substances. If that is true, then if we give these substances orally, the liver has a chance to metabolize them before they get in general circulation and have an opportunity to influence the various tissues of the body; so theoretically and practically the injection method of these estrogens may possibly be more effective.

DR. J. A. CAMPBELL COLSTON (Baltimore, Maryland): In regard to Dr. Smith's inquiry, we are carrying out a study in these cases by serial section of the complete prostate and seminal vesicles, and I hope to be able to report on the results at a later time. Just at present, it is interesting that from the routine pathological examinations that have already been made in six of these cases, we

found viable carcinoma cells in the bases of the seminal vesicles in spite of the fact that rectal palpation had suggested that all disease had satisfactorily regressed in the vesicles.

The changes have been noted after stilbestrol therapy. Vacuolization of the cytoplasm, pyknosis of the nuclei could be seen very easily. It seemed to us that these changes were more pronounced in the periphery than they were in the more central and, therefore, probably older portions of the neoplasm.

SPINAL CORD INJURIES: URETHROGRAPHIC STUDY OF THE BLADDER NECK

GEORGE C. PRATHER, M.D., AND BORIS PETROFF, M.D.
Brookline, Massachusetts

The numerous cases of spinal cord injuries in the recent world war have furnished ample data concerning the urinary tract in a fairly large series. Studies can be made as part of the rehabilitation program for these patients.

Material for this paper was accumulated during duty at two of a number of Army general hospitals in the United States that were designated as centers for men with spinal cord injuries. The 129 cases that form the basis of this report do not represent all the patients with spinal cord injuries admitted to these two hospitals, but they are believed to be representative of a large number.

Although considerable data are available concerning the physiological changes in the bladder following spinal cord injury, most published reports deal with estimates of detrusor activity. We are not aware of a previous study of the bladder neck and posterior urethra in this disorder by urethrographic methods. The object of the study is to record the anatomical status of the bladder neck in patients with traumatic injury of the spinal cord.

X-ray films probably record the findings more impartially than individual cystoscopic interpretation, although both of us have become familiar with the cystoscopic appearance of the lower urinary tract in this type of injury. Anteroposterior urethrograms also probably illustrate the status of the bladder neck and prostatic urethra better than any sphincterometer that is now available. Oblique or third dimensional views have not been taken routinely by us.

The urethrograms done by one of us (G. C. P.) and used for illustrations in this paper were made by retrograde injection from the external meatus with 25 to 30 c.c. opaque media—an amount insufficient to cause contraction of the bladder by distention. They therefore represent a resting urethra and not one undergoing dilatation during contraction of the bladder. The others (by B. P.) were made by injecting opaque media through the external urethral

orifice, applying a penile clamp, and taking the x-ray a few seconds later.

In an attempt to correlate the activity of the detrusor muscle with the bladder neck findings, cystometric studies were done rou-

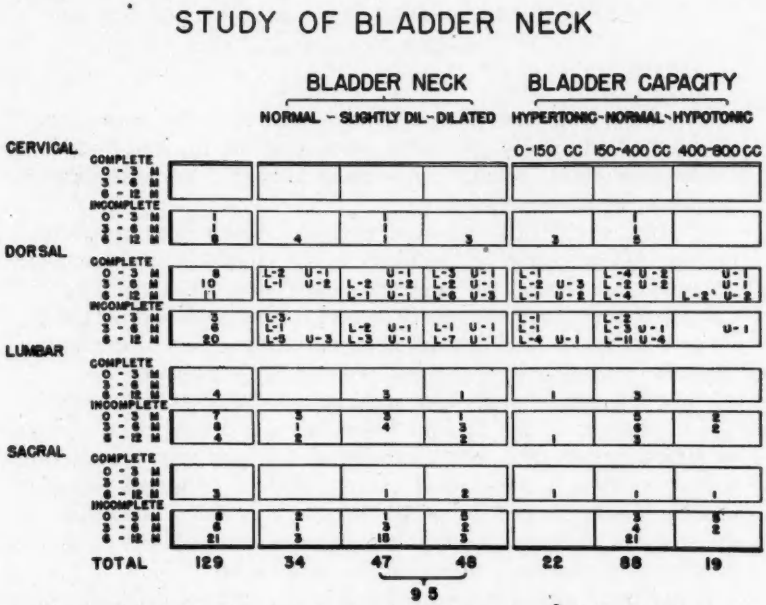

Fig. 1. Spinal cord injuries: Study of bladder neck. Work sheet, 129 cases
Cervical, dorsal, lumbar, and sacral indicate level of injury, nerve level rather than vertebral level.
Complete and incomplete indicate extent of transection of cord.
0 to 3, 3 to 6, 6 to 12 M indicate number of months from injury to time of urethrogram.
L indicates lower half dorsal (thoracic) cord.
U indicates upper half dorsal (thoracic) cord.
Numbers indicate number of cases.
Normal, slightly dilated, and dilated indicate findings by urethrogram.
Hypertonic, normal, hypotonic based simply on bladder capacity, as indicated.

tinely with a water manometer at a date approximating that of the urethrogram. The bladder was filled by constant drip. Cystometric observations are not recorded in this paper.[2]

Knowledge of the condition of the bladder neck in patients with spinal cord injury can be of practical importance as well

as of academic interest. Emmett[1] has assumed "that any lesion which would produce an increase in tone and muscular consistency of the bladder would likewise produce spasticity and hypertrophy

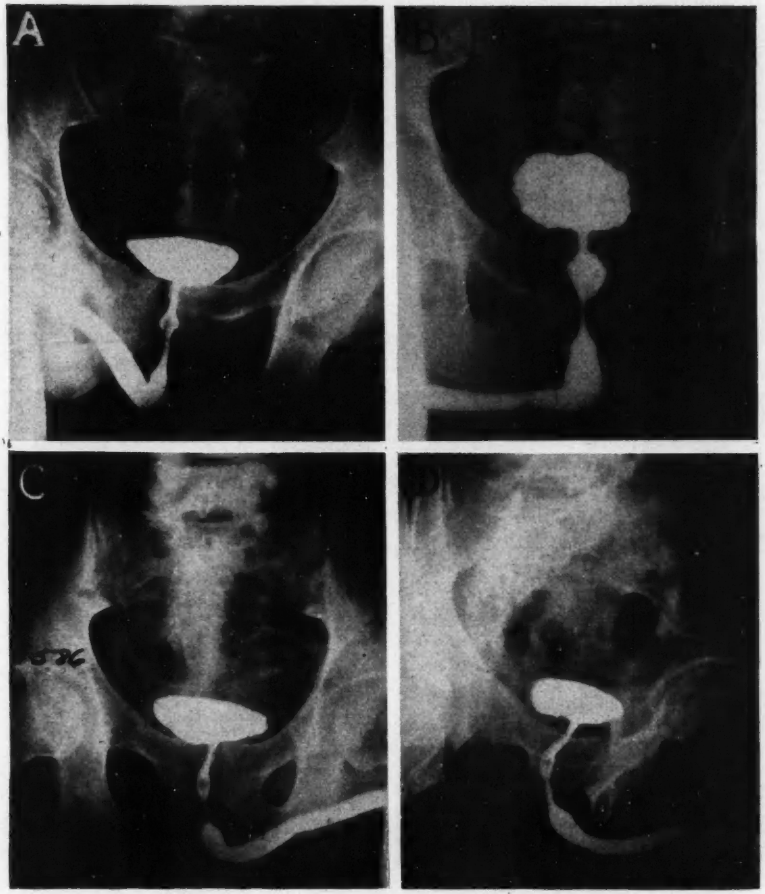

Fig. 2. (*A*) Normal urethrogram in normal young adult without bladder symptoms. (*B*) Urethrogram showing no dilatation of bladder neck. Patient has a complete transection at D 2, is ambulatory in wheelchair and voids by automatic bladder. (*C*) Normal anteroposterior urethrogram in partial cauda equina transection. Patient is ambulatory and voids with voluntary control. (*D*) Oblique urethrogram of patient shown in *C*. There is minimal dilatation of bladder neck.

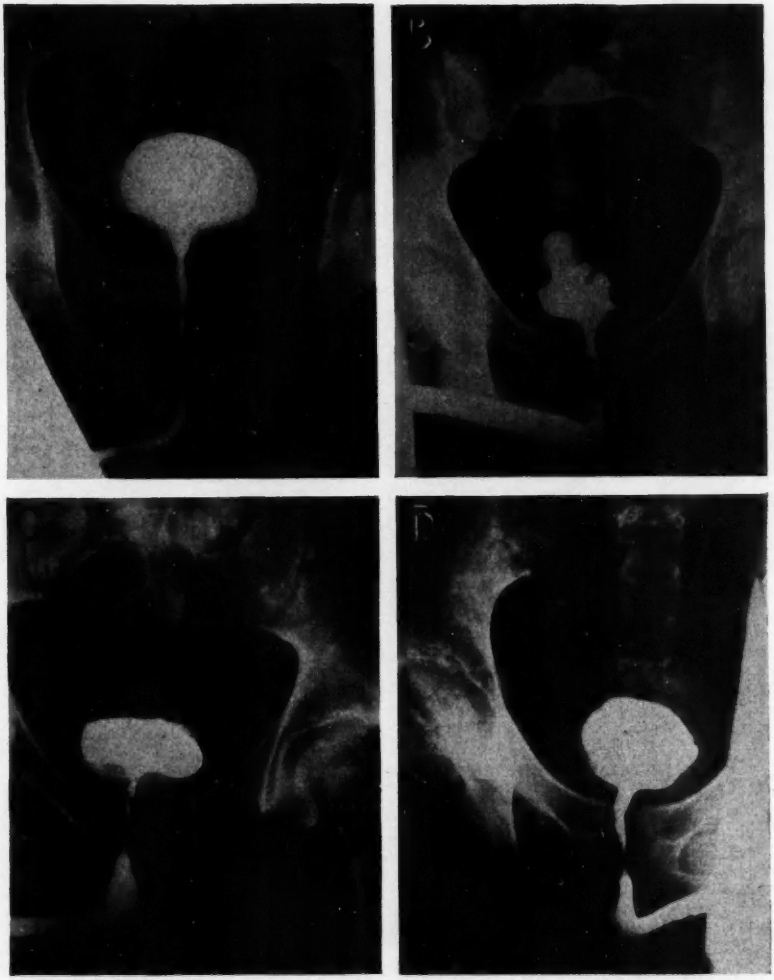

Fig. 3. (*A*) Urethrogram showing slight dilatation of bladder neck. Patient has a complete transection at D 11. Voids per automatic bladder, and is ambulatory in wheelchair. Left ureteral calculus was removed surgically. (*B*) Urethrogram shows slight dilatation of bladder neck. Patient has a complete transection at D 4, is ambulatory, and voids by automatic bladder. (*C*) Urethrogram shows slight dilatation of bladder neck. Patient has partial transection of cervical cord, is ambulatory and voids with voluntary control. (*D*) Urethrogram shows slight dilatation of bladder neck. Patient has complete transection at D 4, is ambulatory in wheelchair and voids by automatic bladder.

of the part of the detrusor which surrounds the bladder neck." On the basis of this assumption he has advocated resection of the bladder neck in this type of disability. Thompson[3] has also advocated resection of the bladder neck in those who have had injury of the

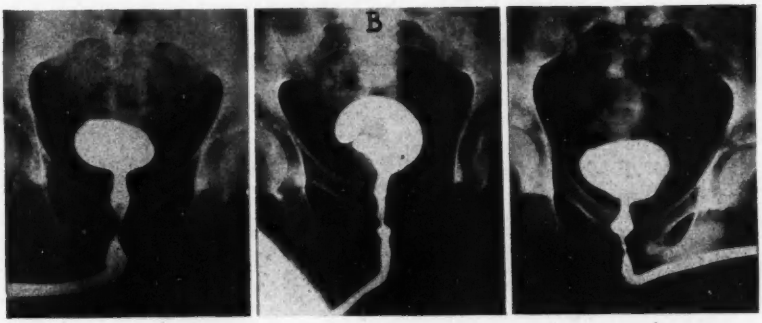

Fig. 4. (*A*) Urethrogram shows dilated bladder neck. Patient has partial transection of cauda equina. (*B*) Urethrogram shows dilated bladder neck. Patient has complete transection at D 6, is ambulatory on braces, but is still on bladder drainage 15 months after injury because of hypotonic bladder. (*C*) Urethrogram shows dilated bladder neck. Patient has partial transection of cauda aquina, is ambulatory on braces and voids by voluntary control, although bladder is somewhat hypotonic.

spinal cord. Experiences with thirty-three cases resected by urologists in Army hospitals have indicated satisfactory results in nineteen and failures in fourteen.

In view of the many assumptions as to the state of the bladder neck in patients with spinal cord injury, it may be of interest to present factual evidence as represented by the cases in this series. Our study has been confined to cases of traumatic injury and includes none with spinal cord disease *per se*. We acknowledge that the presentation of this material is far easier than a physiological interpretation of the findings.

Partial transection of the spinal cord or cauda equina is differentiated by us from complete transection. We believe that this differentiation is extremely important when discussing findings or results. In order to clarify our conception of partial versus complete spinal cord injury the following statements can be made. The cases designated as those with partial transection show some evidence of voluntary motor power and sensory appreciation below the

level of the lesion. The cases designated complete transection show complete functional interruption of the spinal cord at a given level Some of the latter group (complete transection) had visual inspection of the cord during surgery and were found to have complete

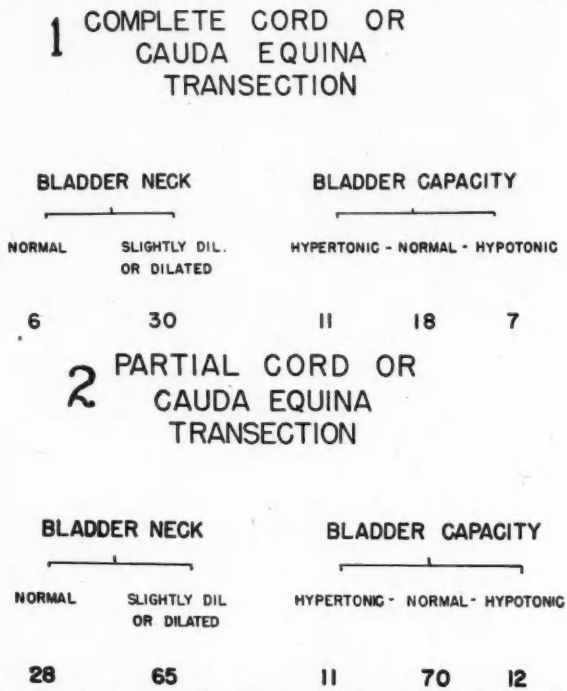

Fig. 5. (*1*) Tabulation of bladder neck findings and bladder capacity in those with complete transection of spinal cord or cauda equina. (*2*) Tabulation of bladder neck findings and bladder capacity in those with partial transection of spinal cord or cauda equina.

interruption of continuity. The remainder have shown no evidence of voluntary motor power or return of sensation below the level of the lesion during a period of at least six months after injury. For estimates of the level and extent of the injury we are indebted to our neurosurgical colleagues, Dr. Charles Elkins and Dr. Cleve Ward.

A tabulation of our 129 cases (Fig. 1) indicates the level of the

injury, its extent (whether complete or incomplete), the approximate time after injury when the urethrographic study was made, the condition of the bladder neck as determined by urethrography, and the bladder capacity as determined during cystometric study.

1 SPINAL CORD AND CAUDA EQUINA INJURIES COMPLETE TRANSECTION

	BLADDER NECK		BLADDER CAPACITY		
	NORMAL	SLIGHTLY DIL. OR DILATED	HYPERTONIC	NORMAL	HYPOTONIC
0-3 MONTHS AFTER INJURY	3	5	1	6	1
3-12 MONTHS AFTER INJURY	3	25	10	12	6

2 SPINAL CORD AND CAUDA EQUINA INJURIES PARTIAL TRANSECTION

	BLADDER NECK		BLADDER CAPACITY		
	NORMAL	SLIGHTLY DIL. OR DILATED	HYPERTONIC	NORMAL	HYPOTONIC
0-3 MONTHS AFTER INJURY	8	11	1	11	7
3-12 MONTHS AFTER INJURY	20	54	10	59	5

Fig. 6. (*1*) Partial transection. Tabulation shows time factor in bladder neck changes. (*2*) Complete transection. Tabulation shows time factor in bladder neck changes.

This represents a work sheet from which smaller groups of cases can be taken for analysis.

The condition of the bladder neck as shown by urethrographic study is designated as normal, slightly dilated, and dilated (Figs. 2, 3, 4). It should be realized that variations both in shape and extent have been found; some of these are illustrated later in this paper.

COMPLETE VERSUS PARTIAL TRANSECTION

The findings in complete transection of the cord or cauda equina are tabulated in Figure 5, *1*. Of thirty-six cases in this group, the bladder neck revealed some degree of dilatation in thirty, a ratio of 5 dilated to 1 normal.

Those with partial transection are tabulated in Figure 5, *2*. Of a total of ninety-three, sixty-five showed dilatation or relaxation of the bladder neck, a ratio of 2.2 dilated to 1 normal.

TIME ELEMENT AS FACTOR IN BLADDER NECK CHANGES

We have not had the opportunity to do urethrographic study on patients immediately after injury or during the following four weeks. Most patients did not reach an Army general hospital in the zone of the interior until two to four months after injury, so that most of the data listed in Figure 6, *1* and *2*, as drawn from cases studied within three months after injury, were actually from cases studied during the second or third month.

Even though our earliest examinations were not made immediately after injury, the time factor appears to have some bearing on the findings. Of eight patients with complete transection examined within three months after injury, urethrograms were normal in three and showed some degree of dilatation in five (Fig. 6, *1*). In a similar group of twenty-eight patients whose initial urethrographic study was made four to twelve months after injury, only three had no dilatation of the bladder neck. Along with this observation is the concomitant finding that the incidence of hypertonic bladder is increased in the group examined more than three months following injury. This association is not absolute, since six cases of hypotonic bladder are included in the same group. Our findings in complete transection of the spinal cord or cauda equina indicate that a greater number of dilated bladder necks are found three to twelve months after injury than two to three months after the accident.

The time element does not appear to be so important in the cases with partial transection of the spinal cord. Of nineteen cases examined within three months of the time of injury, 42 per cent had normal urethrograms, as compared with 27 per cent of those first studied more than three months after injury (Fig. 6, *2*).

LEVEL OF INJURY AS FACTOR IN BLADDER NECK CHANGES

There were no cases in our series with complete transection of the cervical portion of the spinal cord. Those with partial transection in this region are shown in Figure 7, *1*. It is evident that nearly

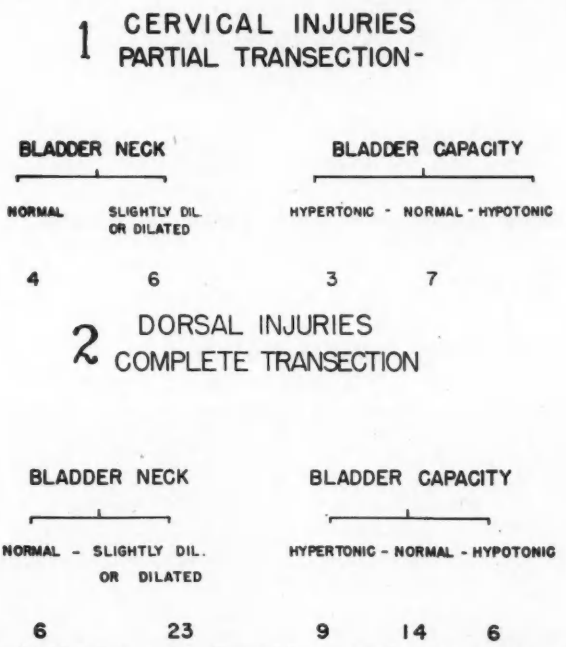

Fig. 7. (*1*) Tabulation of findings in those with partial transection of cervical region of spinal cord. (*2*) Tabulation of findings in those with complete transection of thoracic region of spinal cord.

half of this small group showed no abnormality by urethrogram. Cystometric study was also normal in most of this group.

Twenty-nine cases with complete transection of the thoracic portion of the spinal cord are tabulated in Figure 7, *2*. Dilatation of the bladder neck was present in twenty-three of this group, a ratio of dilated to normal of almost 4 to 1. In partial transection of this same region there was a much higher percentage of normal urethrograms (Fig. 8, *1*). There were also a greater number of cases with

normal bladder capacities in this group than in a group with complete transection at a similar level.

All patients with complete transection of the cauda equina had evidence of some dilatation of the bladder neck (Fig. 8, *2*). Even

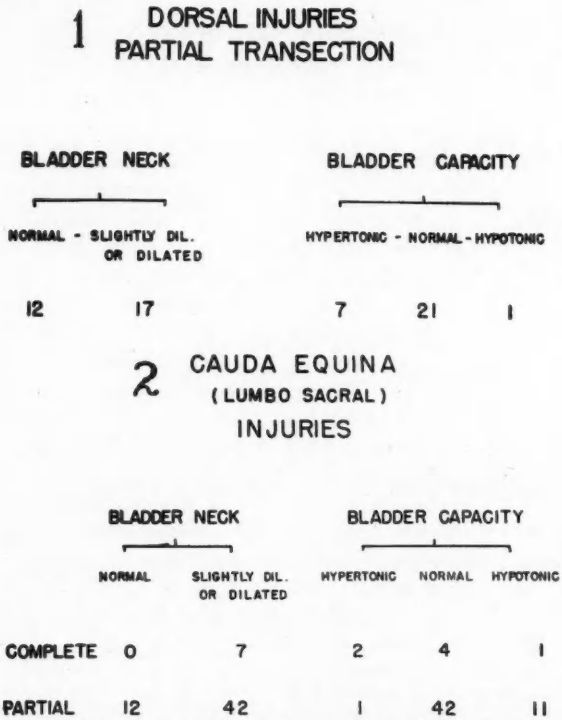

Fig 8. (*1*) Tabulation of findings in those with partial transection of thoracic region of spinal cord. (*2*) Tabulation of findings in those with injuries of cauda equina.

in patients with partial transection in this region there were 3½ times as many with dilated bladder necks as were normal.

It appears that dilatation of the bladder neck is predominant but not constant in those with complete transection of the spinal cord, and that the same finding is always present in complete transection of the cauda equina. In those with partial transection, dilatation of

the bladder neck is common and occurs with increasing frequency from the level of the cervical region to the cauda equina.

TONICITY OF BLADDER AS FACTOR IN BLADDER NECK CHANGES

In order to determine the significance of bladder tone in urethrographic changes of the bladder neck, ten cases with hypertonic blad-

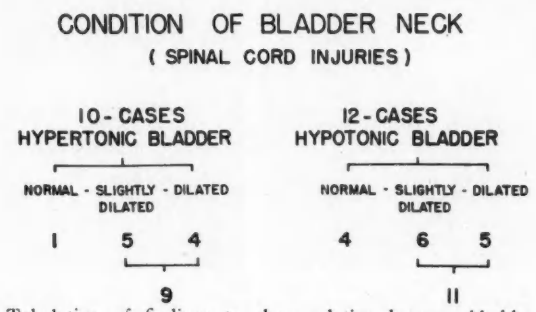

Fig. 9. Tabulation of findings to show relation between bladder neck and bladder capacity.

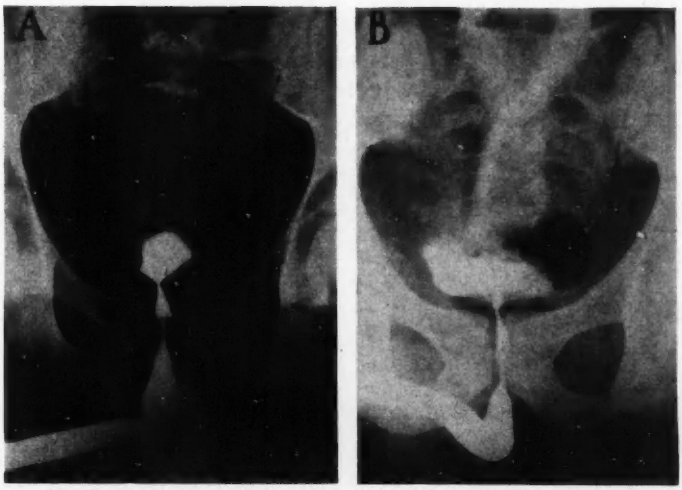

Fig. 10. Patient has complete transection at D 6. Bladder hypertonic. One urethrogram was done in April, 1945, when patient was on suprapubic drainage. Other urethrogram obtained in September, 1945, after several weeks of voiding per automatic bladder.

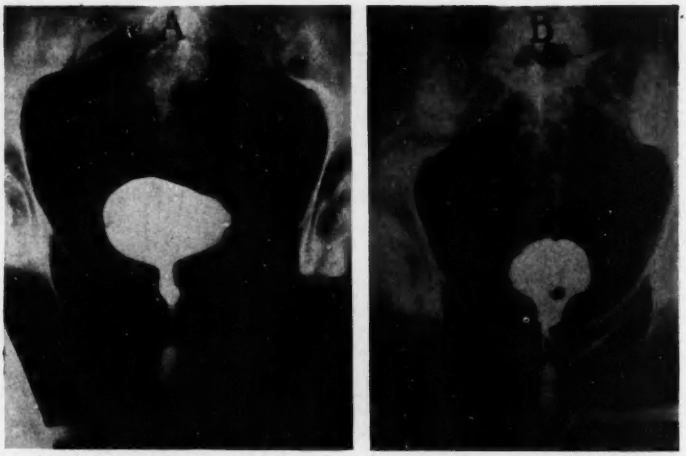

Fig. 11. Patient has complete transection at D 11 and is ambulatory with wheelchair and crutches. One urethrogram obtained in January, 1945, while on suprapubic drainage. Filling defect caused by tube can be seen. Later urethrogram (September, 1945) obtained after several weeks of automatic voiding.

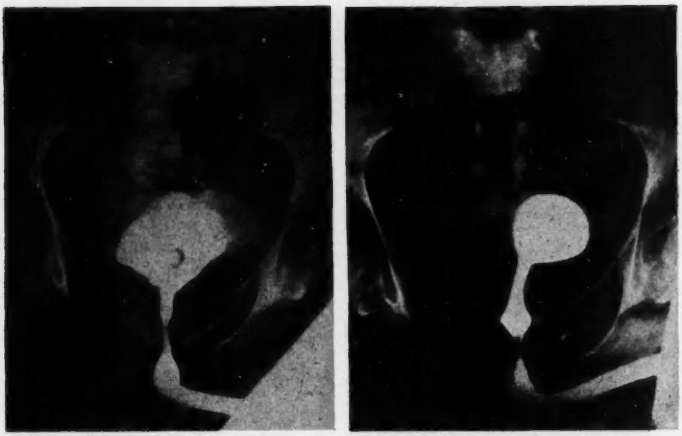

Fig. 12. Patient has partial transection of cauda equina, is ambulatory in wheelchair and with braces. Bladder is hypotonic. One urethrogram made January, 1945, while patient was on drainage. Other urethrogram made nine months later after patient had been voiding a number of weeks with voluntary control.

ders (with a capacity of 150 c.c. or less at cystometric examination) were compared with twelve cases with hypotonic bladders (with a capacity of more than 400 c.c. at cystometric examination). These groups represent cases carefully studied by one of us (G.C.P.). As

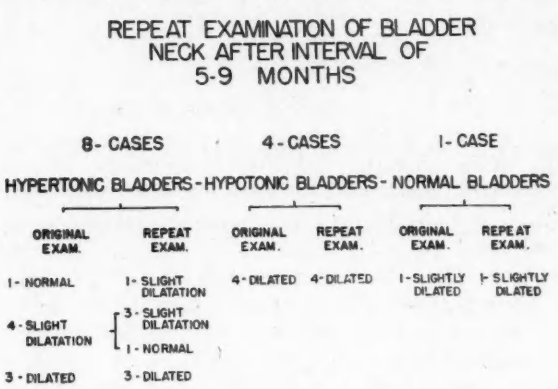

Fig. 13. Findings in repeat examination of bladder neck after interval of five to nine months.

demonstrated in Figure 9, it is evident that some dilatation is prevalent in both the hypertonic and hypotonic type of bladder caused by injury of the spinal cord or cauda equina.

REPEAT EXAMINATION OF THE BLADDER NECK

At the time of the original urethrographic examination our patients had either urethral catheters or suprapubic tubes for drainage of the bladder. Many of these patients later became free of tubes and catheters and voided by automatic bladder (cases with complete transection of the spinal cord or cauda equina) or by voluntary effort (cases with partial transection of the spinal cord or cauda equina). Thirteen patients of this group studied by one of us (G. C. P.) were selected for urethrographic re-examination after an interval of five to nine months to determine whether the condition of the bladder neck had changed. There were ten cases with complete transection and three cases of partial transection. Urethrographic findings in three patients are shown in Figures 10, 11 and 12. The data summarized in Figure 13 shows that while there

may have been some changes in the shape of the prostatic urethra and bladder neck, little or no change in the degree of dilatation was produced by the lapse of time or by change of status of the bladder.

From the data submitted in this paper, it can be seen that dilatation of the bladder neck is a common finding in patients with injury of the spinal cord.

1180 Beacon St., Brookline 46, Mass.

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TRANSURETHRAL RESECTION AND THE PARAPLEGIC

H. C. BUMPUS, JR., M.D.
Pasadena, California

This report is based on observations I made while in charge of the Cord Bladder Service at the United States Naval Hospital at Corona, California. The organization of this service by Dr. G. J. Thompson is of considerable urological interest. While stationed at the United States Naval Hospital at Bethesda, he published in the *Naval Medical Bulletin* the favorable results he had observed in bladder function following transurethral resection in several paraplegic patients. Believing that improvement in the care of such cases would result if they were segregated instead of being treated in general wards, Surgeon General McIntire issued such an order and placed Doctor Thompson in charge. Upon his separation from this service I was ordered as his replacement and and was ably assisted by his former associate, Lt. Comdr. M. H. Nourse, who now has charge of the service.

The formation of such a center not only immediately improved the morale of these patients, for they were quick to appreciate its advantages, but afforded opportunity to evaluate various methods of treating not alone urological problems, but neurological, nutritional, physiotherapeutical and the care of decubitus ulceration, a major complication in this class of patient.

Since the first World War, there has never existed among urologists any uniformity of opinion as to the best method of caring for a cord bladder, the result of spinal cord trauma.

All were in agreement that these patients ultimatedly died of urinary tract infection, but while one school held that this could best be avoided, or at least postponed, by adequate drainage of the urinary tract from the time of injury (the most popular method being that popularized by Doctor Munroe of tidal drainage) another school, equally vocal and positive, placed their trust in the ultimate development among these patients of a virginal automatic bladder never touched by a catheter.

So convinced were they that to catheterize was to condemn to

eternal infection that between the time of injury and the development of automaticity, months later, they were content to let the bladder distend and overflow. Indeed it is an historical fact that so thoroughly was this idea believed that a general hospital order was issued during the first World War forbidding either in this country or abroad, the catheterization of any paraplegic patient in the United States Army.

Dr. Montague L. Boyd, whose duties in the A. E. F. during the war enabled him to critically evaluate its urological practices, writing eight years after the war stated:

"The consensus of medical opinion seems to be that it is best to permit these bladders to distend until they overflow, catheterization is condemned, but I dare say that it is performed in the majority of cases either through ignorance of this opinion or because it would seem that even the infection produced by catheterization could be no worse than the effects of the urinary retention. For some time now I have advocated suprapubic drainage. . . . There are no objections worth mentioning to the employment of the procedure and it has many advantages."

Yet, as the years passed, the dread of sepsis never lessened, and ten years later, in 1937, as the war clouds were again gathering over Europe, there appeared a comprehensive article in the *Journal of Urology* on the care of cord bladders in which the author, A. D. Munger, concluded: "The cord bladder as a result of spinal injury should never be catheterized. If such has occurred, immediate suprapubic drainage is indicated." He reached this conclusion in the belief that where obstruction occurs infection is sure to follow, especially if the relief of the obstruction is attempted by placing a catheter in a urethra the normal resistance of which to infection is lowered by paralysis.

How readily the tissue of these paralyzed patients undergoes pressure necrosis, only those who have cared for their huge decubitus ulcers can appreciate. Even the softest catheter causes trauma and the incidence of periurethral abscesses, epididymitis and prostatitis occurring when catheters are used explains why the development of an automatic bladder is eagerly awaited by some, while others in desperation resort to suprapubic drainage.

Experience in World War II gained by segregating these cases has demonstrated that, while suprapubic drainage remains the best

method for the immediate treatment of battle casualties, it need not be the ultimate means of urinary disposal.

After a lapse of some months, usually from four to five, the majority of paraplegics' bladders develop automaticity. It is the location and severity of the spinal cord injury, not the presence or absence of drainage, that is the determining factor. While this automaticity is developing a suprapubic drain prevents the untoward effects of urinary distention and avoids the hazards of infection and pressure incident to a permanent urethral catheter drainage.

In this group of eighty-seven patients, fifty-eight developed automatic bladders; in thirty-seven of these the action is fully efficient, although in sixteen of them removal of tissue from the bladder neck was necessary before the bladder was able to act efficiently. Included in this group are seven patients who, once the bladder commences to automatically contract, can assist its complete emptying by straining with their abdominal muscles or diaphragm.

Among twenty-one of these fifty-eight patients with automatic bladders, one or two ounces of residual urine may be present most of the time. However, if the urine is clear, it was not thought expedient to attempt to reduce this small amount of residual by transurethral resection. The operations have been reserved for those who are unable to expel any urine or those in which many ounces of residual urine remain after the bladder has automatically contrated.

The reflex center of the bladder emptying mechanism being located in the conus of the cord near the eleventh and twelfth dorsal and first lumbar vertebrae, the height of the injury to the cord predicts in a rough sort of way the type of bladder function that will develop. If the injury is above this point and complete, months later the automatic reflex bladder of infancy returns because no inhibitory impulses from the higher centers are able to function.

On the other hand, if the injury involves the lower lumbar spine, hope of some voluntary control over micturition is warranted for a lesion below the conus leaves the pathway of inhibitory impulses unimpaired and so makes it possible for the bladder to fill without automatically contracting.

Traumatic lesions of the cord are usually followed by more or less spasticity of the bladder muscles and urethral sphincters so that satisfactory emptying of the bladder depends on the ability of

the detrusor muscles to overcome whatever obstruction the sphincteric muscles exert. It is the removal of this obstruction by transurethral resection that enables both the automatic and voluntary types of paraplegic bladders to function. In some cases, where the innervation of the detrusors has been completely or largely destroyed, the patient can empty his bladder by voluntarily increasing his intra-abdominal pressure either by straining or by external suprapubic pressure. The stories of a trigger mechanism or condition reflex where the patient strokes his thigh or pinches his abdomen and his bladder empties has not been observed.

However, only six of those at Corona are dependent upon catheters to get rid of their urine; in most of these a high cervical lesion prevents the use of their hands in the manipulation of their urinals, in some of the others the injury is too recent to determine the type of bladder function that will develop while in a few massive muscle reflexes associated with spasticity prevents, as in the cervical cases, the use of urinals. One of the group using a catheter has been resected three times and is still dependent on intermittent catheter drainage. Attempts at explaining such failures are difficult, but make interesting speculation. Forty-one others, or 46 per cent of the entire group, are more fortunate as they can now voluntarily empty their bladders completely. In twenty-nine of these, transurethral resection was necessary before they could obtain voluntary control.

In these paralyzed patients, healing following resection is slow and late bleeding not infrequent, due to the spasticity of the muscles involved. The removal of a minimum of tissue is recommended even if a second or third resection is required. Three of the cases reported here were resected three times. Even in the case of multiple resection, the total amount of tissue removed is seldom over 10 gm. and frequently less than 5 gm.

It is not the amount of tissue removed, but the establishment of a satisfactory balance by transurethral resection between what expulsive force is still available in the detrusors and the amount of obstruction presented by the internal sphincter that assures functional efficiency in the paraplegic's bladder.

It seems plausible that the hypertonicity that invariably develops in the detrusor muscles (for in all these cases of spinal cord injury the bladder is trabeculated) results in an equal hypertrophy of the

internal sphincter which some consider to be but a specialized edge of the detrusors. It is probably this hypertrophy which acts as an obstruction in preventing paraplegics' bladders from emptying until a portion of it is removed by transurethral resection.

Thirty-three sailors and marines on the Cord Bladder Service at Corona have been awarded the Urological Gold Star. This is placed with fitting ceremony on their bedside charts. These fortunate thirty-three not only empty their bladders, but the urine they pass is sterile to culture—the ultimate goal of ever paraplegic.

112 N. Madison Ave., Pasadena 4, Calif.

DISCUSSION

DR. REED M. NESBIT (Ann Arbor, Michigan): I want to ask some questions of Dr. Bumpus. There were eighty-seven cases reported in that series, and did I get it correctly that you reported that forty-one of the cases void and empty their bladders?

DR. HERMON C. BUMPUS (Pasadena, California): That is right. They divide roughly into two groups, according to the height of the lesion. It doesn't make any difference whether they are confined to bed or whether they are up on their crutches as far as function goes. When the lesion is low in the cord, the majority of those patients void voluntarily with some straining. Others automatically empty when they fill up to the discharging point. If there is so much hypertrophy of the internal sphincter that the bladder can't empty, the transurethral resection straightens it out.

MASSIVE FATAL AIR EMBOLISM FOLLOWING SUPRAPUBIC PROSTATECTOMY

MEREDITH F. CAMPBELL, M.D., and JOHN L. WORK, M.D.
New York City, New York and Montclair, New Jersey

The gravity of air embolism, especially the so-called pulmonary type, has achieved increasing recognition and particularly by surgeons. In the present communication there is reported a case of massive fatal air embolism which occurred two days after uneventful suprapubic prostatectomy in a patient whose bladder was widely open and who was lying quietly in bed. Prolonged search of the medical literature has neither disclosed a similar observation nor given enlightenment as to the genesis of this tragic phenomenon in our patient.

CASE REPORT

An eighty-two-year-old-white man was admitted to Mountainside Hospital, Montclair, New Jersey, on November 21, 1945, because of adenomatous hypertrophy of the prostate gland which had caused increasing symptoms of prostatism during the past year. Overflow incontinence existed for three weeks prior to admission to the hospital. There had been no recent gastrointestinal disturbances but five years previously he had been admitted to the hospital because of lobar pneumonia, phlebitis, and cholecystitis, from which he slowly recovered and was discharged in six weeks. At the time of the prior admission, the urine had shown a "few" to "many" leukocytes, an occasional trace of albumin and because of these findings a diagnosis of chronic pyelonephritis was recorded although no adequate study of the urinary tract was made.

Physical examination at the time of the November, 1945, admission disclosed a remarkably agile and alert aged man. The prostate was three times normal size, smoothly elastic and adenomatous, but with a small nodule on the left margin which was thought might be neoplastic. Indwelling urethral catheter drainage was established, and two days after hospital admission the following laboratory data were obtained: Blood nonprotein nitrogen, 41 mg. per cent; phenolsulphonphthalein excretion, first hour 39 per cent, second hour 20 per cent; a total of 59 per cent. The blood studies showed 11.29 gm. of hemoglobin per 100 c.c. (75.3 per cent), red blood cells 4,760,000 and white blood cells 7,150, with normal cellular distribution.

On indwelling catheterization, the patient became increasingly active, was out of bed most of the time, and on December 3, the thirteen day

in the hospital, under intravenous sodium pentothal anesthesia, bilateral vasectomy and a one-stage suprapubic prostatectomy were performed (M.F.C.). The operation was uneventful, and no hemostatic mechanism such as packing or hemostatic bag was used. The wound was closed loosely around a large Marion tube to keep the bladder open and a Stedman suction pump was attached to the drainage mechanism of the tube. The patient was given 500 c.c. citrated blood and subsequently 1500 c.c. normal saline in 5 per cent dextrose solution. He progressed uneventfully for thirty-six hours when he had a chill at the conclusion of a second infusion. The temperature rose to 102° F., pulse was 88 beats and respirations 14 per minute. He then had a period of asthenia and one of the House Staff made note "seems like Cheyne-Stokes' breathing." The catheter attachment of the Marion tube became obstructed with a small blood clot but this difficulty was readily corrected. The patient became restless, was given pantopon gr. ⅙, and this was repeated three hours later. He became quiet and slightly cyanotic. At six o'clock the second morning (fifty-four hours postoperative) whle lying flat in his bed and receiving early morning care by his nurse, he suddenly became more cyanotic and his respirations more rapid, but he shortly improved without further medication. It seems likely that he might have had a sublethal pulmonary air embolism at this time. One hour and twenty minutes later the respirations again became labored and he suddenly expired. Permission was granted for examination of the thorax and abdomen.

Autopsy summary.—The autopsy was made (J. L. W.) two and one-half hours after death. The body was tall, slender, asthenic, and appeared younger than the purported chronological age of eighty-two years. There was a suprapubic cystotomy wound with a Marion tube still in place, and there was a vasectomy wound on each side. None of these was remarkable. There was no evidence of disruption or excessive wound hemorrhage and there was no crepitation of the skin or subcutaneous tissues about them. There was severe ectasia of the veins of the left lower extremity and there was mild edema of the left foot and ankle.

The usual Y shaped incision was made, the breast plate removed and the pericardium opened. Prompted by the observation of few bubbles in the superior vena cava, and prior to any palpation or manipulation of the viscera, all arteries and veins leading to and from the heart were carefully clamped and ligated, and the heart was removed to be opened subsequently under water. Upon section of the superior and inferior venae cavae above and below the ligatures, bubbles of air were seen in the blood pesent in both veins.

The right atrium and ventricle had a peculiar dilated, yet collapsed appearance. The left atrium was of normal size and the left ventricle was contracted and firm. Numerous large bubbles of air and frothy blood escaped from the right atrium when the heart was opened under water. The fluid blood which remained in the atrium and ventricle was

distinctly foamy and the clotted blood between the trabeculae carneae had a fine spongy texture. Similar soft foamy clot was present in the pulmonary artery and the first portions of its main branches. The foramen ovale was completely spanned by a long, well-developed valve, but was still anatomically patent. There was no air in the left side of the heart or the aorta.

The dissected heart weighed approximately 350 gm. The coronary

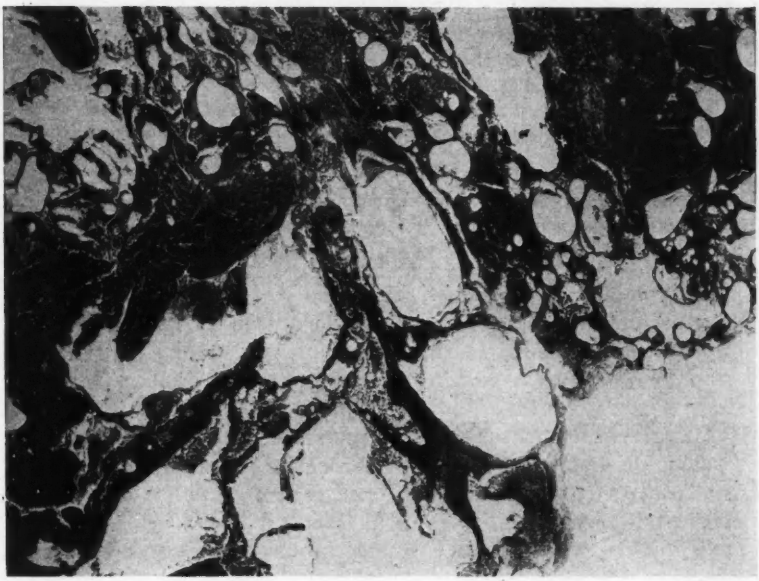

Fig. 1

arteries were the seat of severe arteriosclerosis and there was a large, healed infarct in the anterior and apical aspect of the left ventricle. There was mild thickening of the endocardium above the posterior mitral leaflet. The margins of the aortic cusps were slightly thickened and there were few delicate submarginal adhesions at the commisurs. The tricuspid, pulmonic and mitral valves were normal. There was severe arteriosclerosis of the aorta and its branches.

Microscopic sections through the soft, spongy material in the meshes of the trabeculae carneae and in the pulmonary artery showed postmortem blood clot fenestrated with numerous large and small round clear spaces (Fig. 1).

Both lungs were large, voluminous, soft, and cottony. There were few small emphysematous blebs beneath hyaline plaques of the thick-

ened pleura capping both apices, but there were no large bullae present.

There was moderate arteriolar nephrosclerosis and there was modrate thickening of the walls of the renal calyces and pelvis on the right. The urinary bladder was contracted about the Marion tube and its wall was thickened and edematous. The prostate had been enucleated and the resulting cavity was filled with blood clot limited above by the Marion tube. The mid-sagittal and transverse measurements of the shell of remaining capsule indicated that the gland had been three to four times the normal size. The seminal vesicles were normal. There was no emphysema of the peri-prostatic tissue or of the bladder wall, and no air was demonstrated in the hypogastric or iliac veins. There was mild atrophy of both testicles.

The abnormalities found in other organs are not considered pertinent to this presentation. The more important findings were chronic cholecystitis of mild degree, cholelithiasis, and diverticulum of the colon.

The anatomical diagnosis was: air embolism, recent suprapubic prostatectomy, and arteriosclerosis of the coronary arteries, severe.

COMMENT

Air embolism is generally considered to be one of two types: systemic or pulmonary. The condition known as caisson disease is frequently included in discussions of the subject, but differs from the other two types both in regard to etiology and pathogenesis.

In systemic embolism the gas enters the left side of the heart through the pulmonary veins, or through a patent foramen ovale as a sequence to air in the right heart. The condition is difficult to prove. The symptoms, and death, should it occur, are presumed to be due to an interference of the coronary and/or cerebral circulations.

So-called pulmonary embolism is more frequent, more important, and easier to diagnose, if not clinically, certainly at the autopsy table. The air gains entrance via a systemic vein or veins, is carried to the right heart, and is thence pumped into the pulmonary arteries. The conditions occurs chiefly as a complication of surgical, diagnostic and therapeutic procedures. It may follow such a variety of procedures as the opening of dural sinuses, lavage of paranasal air sinuses, surgical operations about the neck, shoulders and thorax, obstetrical and gynecological procedures and conditions such as Caesarian section, forceps delivery, placenta previa, tubular insufflation (Rubin test), vaginal douching during pregnancy, criminal abortion, and vaginal insufflation for the treatment of vaginitis,

bladder insufflation, perirenal pneumography, and pneumoperitoneum. It has been reported during blood transfusions and infusions, and in connection with phlebotomies on blood donors. Still other cases are recorded in which the portal of entry was not apparent.

The amount of air entering the circulation, and the rate at which it enters are factors of major importance. Death, should it occur, is sudden and is generally conceded to be cardiac rather than respiratory in nature. It has been claimed that the more compressible mixture of blood and air is less readily expelled than normal blood, that the heart becomes filled so as to exclude the normal inflow of blood, and that death occurs due to an interference with proper ventricular contraction. Karsner and others have observed that the injection of sublethal amounts of air into a dog are followed by a fall in blood and pulse pressure from which there is rapid recovery, and that the injection of a final larger amount causes a sudden fall to zero within twenty seconds. Although the evidence is not complete, it seems probable that the sudden contraction of the ventricle upon a compressible mixture so disturbs the normal rhythm as to precipitate ventricular fibrillation, following which sudden death ensues.

Should air enter the cerebral circulation pallor, tonic or clonic convulsions, visual disturbances, temporary blindness, coma, transient manic depressive reactions, amnesia, skin mottling, and nausea are said to occur. Sometimes air bubbles can be identified in the central retinal vessels. In our case, the development of the Cheyne-Stokes'-like breathing for short periods six to twelve hours before death with acute cyanosis and extreme restlessness suggest that this patient may have had cerebral air embolism. Yet it seems more likely that the patient suffered repeated sublethal pulmonary air embolisms which produced the observed symptoms. It is also possible that there may have been cerebral air emboli at this time secondary to air going first through the lungs. Certainly the large amount of air found post mortem in the vena cava, heart and pulmonary circulations must have entered just shortly before the terminal clinical picture developed.

The portal of entry remains unrevealed although it must be assumed to have been bladder or prostatic fossa. Upon returning the patient from the operating room, an 18 F. two-eye catheter was fastened with its tip half way down inside the Marion tube

which in turn acted as a caisson. This catheter was connected with a Stedman pump and it was soon noted that the nurse had erroneously attached the tubing to the discharge or blowing side of the pump; bubbles came out of the Marion tube and the condition was promptly corrected. Because of the extremely low positive pressure these pumps can generate and the fact the bladder and Marion tube were widely open, we do not believe this incident had any relation to events two days later. With this brief and possible exception, no positive pressure was engendered in the bladder to force air up into the venous drainage system and inferior vena cava. The foot of the bed was not elevated, thus eliminating the possible factor of negative pressure causing venous suction. Martland states "in air embolism the exact point of entrance is often not visible, and it is not necessary to see one large open vein." In our case there had been no irrigation of the bladder as a closed cavity, nor had there been an unusual observations at the time of infusion and transfusion. Yet at autopsy the right heart and pulmonary circulations were found filled with embolic air and the characteristic frothy blood clot. Air was also present in the superior and inferior venae cavae.

THERAPY

Prophylaxis against air embolism is meticulous care to prevent the entrance of air into the circulation at the time of surgical, diagnostic, or therapuetic procedures which its occurrence has been known to follow. The only preventive therapy against cerebral air embolism is to keep the patient's head down. To date there is no record of the life of any patient being saved whose heart was pumping air, frothy with blood.

SUMMARY

We are at a loss to explain the mechanism of massive pulmonary air embolism in a man lying quietly in bed, and occurring two days after an uneventful suprapubic prostatectomy and whose bladder was held widely open by a large Marion tube. Autopsy revealed large amounts of air and foamy blood in the caval and pulmonary circulations and right side of the heart. The types, etiologic factors, and pathogenesis of air embolism have been indicated. Treatment is entirely prophylactic.

140 East 54 St., New Yrok, N. Y.
Mountainside Hospital, Montclair, N. J.

DISCUSSION

DR. BENJAMIN S. BARRINGER (New York, N. Y.): May I ask one question? Dr. Campbell spoke so gently, I couldn't tell whether the temporary removal of the suction pump was the cause of the air embolism.

DR. MEREDITH F. CAMPBELL (New York, N. Y.): We didn't think so. I mentioned it only as a possibility. This experience with the Stedman pump occurred immediately postoperative, forty-eight hours or a little longer than that before the man died of acute air embolism. Yet it may have been a factor.

HIGH NON-PROTEIN NITROGEN AND CREATININE

REPORT OF CASES

GEORGE R. LIVERMORE, M.D.
Memphis, Tennessee

Patch and Robinowitz state that patients with chronic nephritis usually show a correlation between the urea nitrogen and the creatinine, while urologic obstructive cases may show a normal or low creatinine content with a high non-protein nitrogren.

I agree with this in the early obstructive urologic cases, but it has been my experience that in cases of long standing, when the back pressure damage to the kidneys has been progressive over a number of years, the creatinine and nonprotein nitrogen both are usually high.

Armando state that hyperphenolemia indicates renal insufficiency, and inasmuch as there exists a certain relation between the amounts of urea and phenol, it may be concluded that in the presence of phenolemia the process is due to retention if that relation exists and that the process is extrarenal when there is a hyperurea with a normal phenolemia and that the process is mixed if the retention of nitrogenous substances exceeds that of phenol.

I regret that I had not seen the article by Armand before we treated the case of Mrs. G., because tests for phenol would have been made. Both Dr. Rudner and I believed that we were dealing with a renal and an extra-renal uremia. Derow states that postoperative rises of blood non-protein nitrogen in patients with normal renal function may be due to:

(A) Oliguria as a result of
1. Insufficient water available for urine formation as a consequence of operative and postoperative water losses.
2. Prolonged postoperative use of pituitary extract (Pitressin).
3. Lowering of blood pressure associated with shock and spinal anesthesia.
4. Heart failure.

(B) Increased destruction of body protein accompanying the operation and postoperative period.
(C) Acute nephritis (liver, kidney syndrome).
(D) Post-renal obstructive anuria. As a preventive Derow suggests a daily output of at least 1,500 c.c. urine. Normal saline should be given orally, by clysis or intravenously in sufficient quantity to insure 1,500 c.c. output. Glucose solution not only supplies fluid but will lessen the toxic destruction of protein by supplying carbohydrate and will prevent acidoses.

I would add, however, that we should be careful to check the blood chlorides for fear of causing an alkalosis, especially where nausea, vomiting and diarrhoea cause dehydration, and that Hartman's solution or soda bicarbonate, as suggested by Pearse, be alternated with glucose in saline intravenously.

Vollard says numerous factors besides true kidney disease influence the level of blood urea and non-protein nitrogen; e.g., cardiac decompensation, probably through slowing the renal circulation and oliguria; fever, infections, surgical intervention, acting by overdestruction of body protein and, I would add, by lowering blood pressure, a factor that is often overlooked in our enthusiasm to force fluids. He also says in cases with enormous losses of water and salt by vomiting or diarrhea (cholera, paratyphoid), he has observed values for non-protein nitrogen as high as 200 to 300 mg. per 100 c.c. blood; values found otherwise only in true uremia.

Kolmer says (and we know it is true) that an increase of creatinine may occur in any condition in which the urea nitrogen is increased. Indeed a retention of 5 or more mg. per 100 c.c. blood indicates a grave prognosis. In urinary tract obstruction without permanent renal damage, extremely large amounts of creatinine may return to normal following relief of obstruction. Two of the cases reported are of this type. We see this repeatedly exemplified in prostatic hypertrophy and bilateral ureteral obstruction from any cause. The degree of increased creatinine is proportional to that of urea nitrogen except in chronic glomerulonephritis in which a high urea nitrogen may be observed in association with a normal creatinine. Creatinine may be increased in uremia, acute or chronic nephritis, in acute high fevers of infection, vomiting and diarrhea, profuse sweating and alkalosis following operations and extensive

burns, in shock and diminution of fluid intake, severe congestive heart failure, urinary tract obstruction and sometimes in pregnancy, usually after the sixth month, and Myers adds intestinal obstruction.

In recent years the possibility of the cause of uremia is the accumulation in the blood of putrefactive intestinal products, phenol, paracresol, indol, et cetera. Also there is the possibility of another toxic substance, guanidine, probably a product of abnormal protein metabolism due to hepatic insufficiency.

Steinberg reports a rise of non-protein nitrogen in coronary thrombosis.

Reflex anuria, whether due to calculi in one ureter or kidney, with the other kidney normal, trauma from dilation of the ureter and catheterization and instrumentation of the ureters, usually clears up readily after relief of the obstruction and appropriate treatment consisting of forced fluids, Hartman's solution, 5 per cent glucose in saline or as Robin Pearse advocates, sodium bicarbonate intravenously, cholagogue and hydragogue purgatives hot packs over the kidneys, sweating and adequate support of the blood pressure.

Myers reports a case of reflex anuria, following unilateral pyelogram and displacement of a renal calculus in which the blood creatinine rose to 23.1. The patient recovered under alkali therapy and forced fluids through a duodenal tube. The re-establishment of good urinary output does not always indicate that the battle is won. Hamer and Mertz report two fatal cases in which free diuresis had been produced but with no diminution in the blood non-protein nitrogen. I also cite such a case.

In cases of this type the function of the kidneys is so poor, and its ability to excrete nitrogenous products so limited that it cannot reduce the excess non-protein nitrogen in the blood. Mercury, phenol compounds, arsenic and even bismuth may cause this type. In such cases we have three factors to consider: (1) shock, (2) damage to the kidneys, and (3) damage to the mouth, esophagus, stomach and intestines, with toxic absorption from necrotic tissues. In these cases, antidotes for the specific poison, albumins, white of egg and milk in bichloride; ferric hydrate with magnesia at once and later olive oil and milk in arsenic; also sodium thiosulphate intravenously, together with stimulation, forced fluids, Hartman's

solution and glucose intravenously and gastric, duodenal and colon lavage with soda bicarbonate solution. In phenol poisoning the antidote is alcohol or whiskey.

We all know that sulfa drugs may occlude the ureter and renal tubules and give rise to anuria and death if the blockage is not removed. Hamer and Mertz report a case of fatal anuria following sulfapyridine administration for pneumonia. The crystals in the tubules were thought to be acetyl sulfapyridine but on chemical examination were found to be uric acid and urates. Since alkalies are now given routinely with the sulfa drugs these cases should become a rarity.

I herewith report a similar case:

A white man, aged thirty, had influenza and was given sulfathiazole for three days. The exact amount was not known but no alkalies were given with it. The following day (fourth day of his illness) he voided only 90 c.c. urine and the following three days he was completely anuric. He was catheterized and as no urine was obtained he was referred to me. When he reached the hospital he was in almost complete coma; his blood pressure was 150/80, non-protein nitrogen 256 mg., creatinine 13 mg. per 100 c.c. blood. About 1 dram of urine had drained from the retention catheter. He was put on the treatment outlined above. The following twelve hours his output was 300 c.c.; a urinalysis showed specific gravity 1.015, acid, albumin 3 plus, hyaline, granular and waxy casts. At this time he was fairly rational. The same treatment continued. The next twelve hours his output was 450 c.c. and he was completely rational. That afternoon his blood pressure dropped to 90/50; he lapsed into deep coma with labored and stertorous respiration, pulse 120 and weak volume. Despite stimulation with caffeine sodium benzoate gr. 7½, digifolin 1 c.c., alternating every three hours, adrenalin and coramine intravenously, his heart gradually failed, and he died six hours after the sudden drop in blood pressure.

Lyons and Raines report a case of oliguria with delirium, edema and constant vomiting, non-protein nitrogen 100, creatinine 2.7, following a blood transfusion three days previously in which decapsulation was done on one kidney with recovery. He had voided only 90 c.c. in the forty-eight hours preceding decapsulation and only 80 c.c. the first twenty-four hours after it; 368 c.c. the second twenty-four hours, 2,120 c.c. in the third twenty-four hours, and in the fourth twenty-four hours 5,010 c.c.

Two new methods of treatment for uremia have appeared in recent literature. Frank, Seligman and Fine report a case of uremia

of ten days' oliguria; three days of 30 c.c. per day and last four days of 30 c.c. 200 c.c., 0 c.c., and 0 c.c., respectively. The patient recovered under peritoneal irrigations with Tyrode's solution with glucose to which penicillin was added for bacteriostasis, and heparin to prevent fibrin deposition in the peritoneal cavity. Snapper, in a letter to the editor of the *Journal of the American Medical Association* May 18, 1946, comments on Frank, Seligman and Fine's report and states that Dr. W. J. Kolff has obtained comparable results with an artificial kidney. This consists of a cellophane tube 23 mm. wide and 50 yards long, which is wound around a wooden latticed cylinder. The cylinder rotates slowly and the lowest part of it is submerged in a tank containing 70 to 100 litres of a solution of 0.6 per cent sodium chloride, 0.2 per cent sodium bicarbonate, 0.04 per cent potassium chloride and 1.5 to 2 per cent glucose.

Twelve hundred milligrams or more of heparin are also given. One end of the cellophane tube is connected with a canula in the radial artery and the other to a cannula in a vein.

CASE REPORTS

Case 1.—R. S., a white man, married, aged sixty-five, had a hypertrophied prostate with symptoms dating back one year. The heart and lungs were normal; the blood pressure 95/68. His general physical condition was good.

A 16 F Foley bag catheter was passed and 1½ ounces residual urine obtained. The bladder was decompressed. During the first twenty-four hours the output was 300 c.c. Cystoscopy disclosed a collar, median bar and bilateral intraurethral hypertrophy grade II. A plain film was negative. The urine was clear, acid reaction, specific gravity 1.002, and a few white and red blood cells. The Foley bag catheter was replaced and 1,000 c.c. 5 per cent glucose in saline given intravenously. During the next twenty-four hours the output was 525 c.c., the next twenty-four hours, 700 c.c., but the patient was definitely uremic, somnolent and incoherent. The blood pressure was 120/80; the phthalein output the first hour 5 per cent, the second hour minus 5 per cent. The non-protein nitrogen was 200 and creatinine 9. Hartman's solution and 5 per cent glucose in saline, 1,000 c.c. intravenously, were alternated every six hours, caffeine sodium benzonate gr. 7½ every six hours, calomel gr. ½ every half hour for six doses, followed in two hours by magnesium sulphate. Hot packs over kidneys. The output of urine increased to 850 c.c. The output rapidly increased and in two more days he was mentally clear, the urine output was 2,000 c.c. in twenty-four hours, and the non-protein nitrogen and creatinine were 33 and 1.54 respectively. Six days later a transurethral prostatic resection was done, and he made an uneventful recovery.

Case 2.—J. T., a white man aged forty-eight, had acute cholecystitis for which he was given sulfathiazole four days before entering the hospital. He was said to have taken 2 gm. every three hours for three doses, then 1 gm. every three hours for two days, a total of 22 gm. in about thirty hours. No alkalies were given with the sulfathiazole.

When first seen he had a papular rash over his body, arms and legs. He had had a rigor and his temperature was 100.4.° His family stated he had passed only about 100 c.c. urine in the past twenty-four hours. The non-protein nitrogen was 44 mg. per 100 c.c. blood; the blood pressure 144/90. Urinalysis: albumin 2 plus, granular and waxy casts, 2 to 4 blood cells and many pus cells to the high power field. He was put on intravenous 5 per cent glucose in saline, 1,000 c.c. every eight hours, forced fluids, and delvinal sodium gr. 3 p.r.n.

Cystoscopy was performed August 23, 1945. No crystals were seen and the catheter passed eisily to each pelvis, but there was no drip from either kidney. Both catheters were left in place, but x-ray and pyelograms were made with negative findings. (The making of pyelograms was unwise.) On August 24 the blood pressure was 146/78. The patient was put on caffeine sodium benzoate gr. 7½ every six hours. He became delirious. There was no output of urine.

On August 25 there was no urine output. Glucose, 50 c.c. of a 50 per cent solution, was given intravenously, and also aminophyllin, gr. 5 intravenously. The catheters were removed because they were not draining. The non-protein nitrogen was 165 mg. per 100 c.c. blood. Penicillin, 20,000 units every three hours intramuscularly, was begun because the patient has an irregular temperature (100° to 102°) and there was some pulmonary edema and edema of dependent portions of body, feet and legs. The blood pressure was 160/90.

On August 26 the patient voided 400 c.c. dark brown urine. Glucose, 25 c.c. of 25 per cent, was given intravenously. The blood pressure varied from 135/95 to 160/90.

On August 28 there was no urinary output. I was called in consultation. The non-protein nitrogen was 168. Pulmonary edema was present in both bases; the feet and legs and face were edematous, and also dependent portions of body and thighs. I ordered Hartman's solution, 1,000 c.c., alternating with 5 per cent glucose in saline every eight hours. During the next twelve hours the patient voided 100 c.c. urine.

On August 29 the urinary output was 500 c.c. The pulmonary edema had increased. Calomel and magnesium sulphate were ordered. Caffeine sodium benzoate was continued.

On August 30 the urinary output was 1,200 c.c., the non-protein nitrogen was 267, creatinine 12. The extensive rash was still present. The blood sugar was 91 mg.

On August 31 the output was 1,400 c.c.

On September 1 the output was 4,100 c.c., the non-protein nitrogen 195.5, creatine 9.9. The patient was voiding freely, the edema cleared.

On September 7, the non-protein nitrogen was 45 and creatinine 3.5. He continued to improve and was discharged September 10. The non-protein nitrogen was 40 and creatinine 2.1.

Case 3.—Mrs. E. G., a white woman, married, aged thirty-five, had had chronic mastoiditis with two discharging sinuses following a mastoid operation in February, 1944. An abscessed tooth had been removed four days before admission to the hospital. The dentist had given her sulfathiazole. She took six tablets, then began vomiting and had been unable to retain anything since. She had two or three rigors, and the temperature that day was 105°. She had continued to have rigors and fever ever since. The patient was somnolent, the non-protein nitrogen 82.1. The blood was negative for malaria; blood culture was negative. Penicillin, 25,000 units, was given intramuscularly every three hours. The output of urine was 210 c.c.; next day it was 8 c.c. The patient became comatose and continued in same condition for three days when I was asked to see her.

No. 6 catheters were passed to each kidney. There was no flow from the right, a few drops from the left; no crystals were seen. The non-protein nitrogen was 126. The next day the non-protein nitrogen was 138, creatinine 10.4. Edema developed in both lungs and in the dependent portions of the body, thighs and legs. The catheters drained 15 c.c. urine and slipped out the next day. Calomel and magnesium sulphate were given. The catheters were replaced and output was 12 c.c. from catheters, 500 c.c. pale urine from bladder; next day, catheters 21 c.c., bladder 1,000 c.c.; next day, catheters 40 c.c., bladder 1,200 c.c., next day output 1,700 c.c., non-protein nitrogen 123.6, creatinine 8.8. The output of urine continued to increase until ten days later when the non-protein nitrogen was 101.5 and creatinine 4.6. This dropped to 77.8 and 2.4 respectively in another four days and one week later was 38 and 1.75. The patient was seen four weeks ago and was in perfect health.

Medical Arts Bldg., Memphis, Tenn.

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